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(54) Title: ACYCLIC AND CYCLIC AMINE DERIVATIVES

(57) Abstract: The present invention relates to acyclic and cyclic amine derivatives for treating or preventing neuronal damage associated with neurological diseases. The invention also provides compositions comprising the compounds of the present invention and methods of utilizing those compositions for treating or preventing neuronal damage.

ACYCLIC AND CYCLIC AMINE DERIVATIVES

TECHNICAL FIELD OF THE INVENTION

The present invention relates to acyclic and cyclic amine derivatives for treating or preventing neuronal damage associated with neurological diseases. The invention also provides compositions comprising the compounds of the present invention and methods of utilizing those compositions for treating or preventing neuronal damage.

BACKGROUND OF THE INVENTION

Neurological diseases are associated with the death of or injury to neuronal cells. Typical treatment of neurological diseases involves drugs capable of inhibiting neuronal cell death. A more recent approach involves the promotion of nerve regeneration by promoting neuronal growth.

Neuronal growth, which is critical for the survival of neurons, is stimulated *in vitro* by nerve growth factors (NGF). For example, Glial Cell Line-Derived Neurotrophic Factor (GDNF) demonstrates neurotrophic activity both, *in vivo* and *in vitro*, and is currently being investigated for the treatment of Parkinson's disease. Insulin and insulin-like growth factors have been shown to stimulate growth of neurites in rat pheochromocytoma PC12 cells and in cultured sympathetic and sensory neurons [Recio-Pinto et al., J. Neurosci., 6, pp. 1211-1219 (1986)]. Insulin and insulin-like growth factors also stimulate the

regeneration of injured motor nerves *in vivo* and *in vitro* [Near et al., Proc. Natl. Acad. Sci., pp. 89, 11716-11720 (1992); and Edbladh et al., Brain Res., 641, pp. 76-82 (1994)]. Similarly, fibroblast growth factor (FGF) stimulates neural proliferation [D. Gospodarowicz et al., Cell Differ., 19, p. 1 (1986)] and growth [M. A. Walter et al., Lymphokine Cytokine Res., 12, p. 135 (1993)].

There are, however, several disadvantages associated with the use of nerve growth factors for treating neurological diseases. They do not readily cross the blood-brain barrier. They are unstable in plasma and they have poor drug delivery properties.

Recently, small molecules have been shown to stimulate neurite outgrowth *in vivo*. In individuals suffering from a neurological disease, this stimulation of neuronal growth protects neurons from further degeneration, and accelerates the regeneration of nerve cells. For example, estrogen has been shown to promote the growth of axons and dendrites, which are neurites sent out by nerve cells to communicate with each other in a developing or injured adult brain [(C. Dominique Toran-Allerand et al., J. Steroid Biochem. Mol. Biol., 56, pp. 169-78 (1996); and B. S. McEwen et al., Brain Res. Dev. Brain. Res., 87, pp. 91-95 (1995)]. The progress of Alzheimer's disease is slowed in women who take estrogen. Estrogen is hypothesized to complement NGF and other neurotrophins and thereby help neurons differentiate and survive.

Other target sites for the treatment of neurodegenerative disease are the immunophilin class of proteins. Immunophilins are a family of soluble proteins

that mediate the actions of immunosuppressant drugs such as cyclosporin A, FK506 and rapamycin. Of particular interest is the 12 kDa immunophilin, FK-506 binding protein (FKBP12). FKBP12 binds FK-506 and rapamycin, leading to an inhibition of T-cell activation and proliferation. Interestingly, the mechanism of action of FK-506 and rapamycin are different. For a review, see, S. H. Solomon et al., Nature Med., 1, pp. 32-37 (1995). It has been reported that compounds with an affinity for FKBP12 that inhibit that protein's rotomase activity possess nerve growth stimulatory activity. [Lyons et al., Proc. Natl. Acad. Sci. USA, 91, pp. 3191-3195 (1994)]. Many of these such compounds also have immunosuppressive activity.

FK506 (Tacrolimus) has been demonstrated to act synergistically with NGF in stimulating neurite outgrowth in PC12 cells as well as sensory ganglia [Lyons et al. (1994)]. This compound has also been shown to be neuroprotective in focal cerebral ischemia [J. Sharkey and S. P. Butcher, Nature, 371, pp. 336-339 (1994)] and to increase the rate of axonal regeneration in injured sciatic nerve [B. Gold et al., J. Neurosci., 15, pp. 7509-16 (1995)].

The use of immunosuppressive compounds, however, has drawbacks in that prolonged treatment with these compounds can cause nephrotoxicity [Kopp et al., J. Am. Soc. Nephrol., 1, p. 162 (1991)], neurological deficits [P.C. DeGroen et al., N. Eng. J. Med., 317, p. 861 (1987)] and vascular hypertension [Kahan et al., N. Eng. J. Med., 321, p. 1725 (1989)].

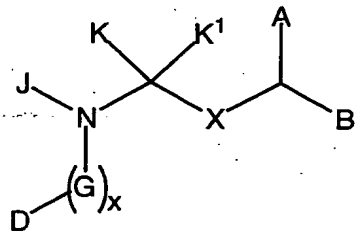
More recently, sub-classes of FKBP binding compounds which inhibit rotomase activity, but which purportedly lack immunosuppressive function have been disclosed for use in stimulating nerve growth [see, United States patent 5,614,547; WO 96/40633; WO 96/40140; WO 97/16190; J. P. Steiner et al., Proc. Natl. Acad. Sci. USA , 94, pp. 2019-23 (1997); and G. S. Hamilton et al., Bioorg. Med. Chem. Lett., 7, pp. 1785-90 (1997)].

Stimulation of neural axons in nerve cells by piperidine derivatives is described in WO 96/41609. Clinical use of the piperidine and pyrrolidine derivatives known so far for stimulating axonal growth has not been promising, as the compounds are unstable in plasma and do not pass the blood-brain barrier in adequate amounts.

Though a wide variety of neurological degenerative diseases may be treated by promoting repair of neuronal damage, there are relatively few agents known to possess these properties. Thus, there remains a need for new compounds and compositions that have the ability to either prevent or treat neuronal damage associated with neuropathologic disorders.

SUMMARY OF THE INVENTION

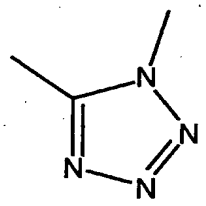
The invention provides compounds of formula (I):



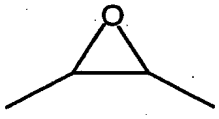
(I)

and pharmaceutically acceptable derivatives thereof, wherein:

X is selected from $-CH_2CH_2-$, $-CH=CH-$, $-C(OH)CH_2-$, $-CH_2C(OH)-$, $=C(F)CH_2-$, $-C(F)=CH_2-$, $-NHC(O)-$, $-P(O)(OH)CH_2-$, $-CH_2S(O)_2-$, $-C(S)NR^1-$, $-C(O)CH_2CH(OH)-$, $-C(OH)CF_2-$, $-C(O)CF_2-$, $-CH(F)CH_2-$, $-C(F)_2CH_2-$, $-CH_2CH(F)-$, $-CH_2C(F)_2-$



or



A, B and R^1 are independently E, (C_1-C_{10})-straight or branched alkyl, (C_2-C_{10})-straight or branched alkenyl or alkynyl, or (C_5-C_7)-cycloalkyl or cycloalkenyl; wherein 1 or 2 hydrogen atoms in said alkyl, alkenyl or alkynyl are optionally and independently replaced with E, (C_5-C_7)-cycloalkyl or cycloalkenyl; and wherein 1 to 2 of the $-CH_2-$ groups in said alkyl, alkenyl, or alkynyl groups is optionally and independently replaced by -O-, -S-, $-S(O)-$, $-S(O)_2-$, $=N-$, $-N=$ or $-N(R^3)-$;

or, B and R^1 are independently hydrogen;

R^3 is hydrogen, (C_1-C_4)-straight or branched alkyl, (C_3-C_4)-straight or branched alkenyl or alkynyl, or (C_1-C_4) bridging alkyl, wherein a bridge is formed between the nitrogen atom to which said R^3 is bound and any carbon atom of said alkyl, alkenyl or alkynyl to form a ring, and wherein said ring is optionally benzofused;

E is a saturated, partially saturated or unsaturated, or aromatic monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms

independently selected from C, N, $N(R^3)$, O, S, S(O), or $S(O)_2$; and wherein no more than 4 ring atoms are selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$;

wherein 1 to 4 hydrogen atoms in E are optionally and independently replaced with halogen, hydroxyl, hydroxymethyl, nitro, SO_3H, trifluoromethyl, trifluoromethoxy, (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl, O-[(C_1-C_6)-straight or branched alkyl], O-[(C_3-C_6)-straight or branched alkenyl], $(CH_2)_n-N(R^4)(R^5)$, $(CH_2)_n-NH(R^4)-(CH_2)_n-Z$, $(CH_2)_n-N(R^4-(CH_2)_n-Z)(R^5-(CH_2)_n-Z)$, $(CH_2)_n-Z$, $O-(CH_2)_n-Z$, $(CH_2)_n-O-Z$, $S-(CH_2)_n-Z$, CH=CH-Z, 1,2-methylenedioxy, C(O)OH, C(O)O-[(C_1-C_6)-straight or branched alkyl], $C(O)O-(CH_2)_n-Z$ or $C(O)-N(R^4)(R^5)$;

each of R^4 and R^5 are independently hydrogen, (C_1-C_6)-straight or branched alkyl, (C_3-C_5)-straight or branched alkenyl, or wherein R^4 and R^5, when bound to the same nitrogen atom, are taken together with the nitrogen atom to form a 5 or 6 membered ring, wherein said ring optionally contains 1 to 3 additional heteroatoms independently selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$; wherein said alkyl, alkenyl or alkynyl groups in R_4 and R_5 are optionally substituted with Z.

each n is independently 0 to 4;

each Z is independently selected from a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms independently selected from C, N, $N(R^3)$, O, S, S(O), or $S(O)_2$; and wherein no more than 4 ring atoms are selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$;

wherein 1 to 4 hydrogen atoms in Z are optionally

and independently replaced with halo, hydroxy, nitro, cyano, C(O)OH, (C_1-C_3)-straight or branched alkyl, O-(C_1-C_3)-straight or branched alkyl, C(O)O-[(C_1-C_3)-straight or branched alkyl], amino, NH[(C_1-C_3)-straight or branched alkyl], or N-[(C_1-C_3)-straight or branched alkyl]$_2$;

J is H, methyl, ethyl or benzyl;

K and K^1 are independently selected from (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl or alkynyl, or cyclohexylmethyl, wherein 1 to 2 hydrogen atoms in said alkyl, alkenyl or alkynyl is optionally and independently replaced with E;

wherein K and K^1 are independently and optionally substituted with up to 3 substituents selected from halogen, OH, O-(C_1-C_6)-alkyl, O-(CH_2)n-Z, NO_2, C(O)OH, C(O)-O-(C_1-C_6)-alkyl, C(O)NR^4R^5, NR^4R^5 and $(CH_2)_n$-Z; or,

J and K, taken together with the nitrogen and carbon atom to which they are respectively bound, form a 5-7 membered heterocyclic ring, optionally containing up to 3 additional heteroatoms selected from N, N(R^3), O, S, S(O), or S(O)$_2$, wherein 1 to 4 hydrogen atoms in said heterocyclic ring are optionally and independently replaced with (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl or alkynyl, oxo, hydroxyl or Z; and wherein any -CH_2- group in said alkyl, alkenyl or alkynyl substituent is optionally and independently replaced by -O-, -S-, -S(O)-, -S(O$_2$)-, =N-, -N=, or -N(R^3)-; and wherein said heterocyclic ring is optionally fused with E;

G, when present, is -S(O)$_2$-, -C(O)-, -S(O)$_2$-Y-, -C(O)-Y-, -C(O)-C(O)-, or -C(O)-C(O)-Y-;

Y is oxygen, or $N(R^6)$;

wherein R^6 is hydrogen, E, (C_1-C_6)-straight or branched alkyl, (C_3-C_6)-straight or branched alkenyl or alkynyl; or wherein R^6 and D are taken together with the atoms to which they are bound to form a 5 to 7 membered ring system wherein said ring optionally contains 1 to 3 additional heteroatoms independently selected from O, S, N, $N(R^3)$, SO, or SO_2; and wherein said ring is optionally benzofused;

D is hydrogen, (C_1-C_7)-straight or branched alkyl, (C_2-C_7)-straight or branched alkenyl or alkynyl, (C_5-C_7)-cycloalkyl or cycloalkenyl optionally substituted with (C_1-C_6)-straight or branched alkyl or (C_2-C_7)-straight or branched alkenyl or alkynyl, $[(C_1-C_7)$-alkyl$]$-E, $[(C_2-C_7)$-alkenyl or alkynyl$]$-E, or E;

wherein 1 to 2 of the CH_2 groups of said alkyl, alkenyl or alkynyl chains in D is optionally replaced by -O-, -S-, -S(O)-, $-S(O_2)-$, =N-, -N=, or $-N(R^3)$;

provided that when J is hydrogen or G is selected from $-S(O)_2-$, C(O)C(O)-, SO_2-Y, C(O)-Y, or C(O)C(O)-Y, wherein Y is O; then D is not hydrogen; and

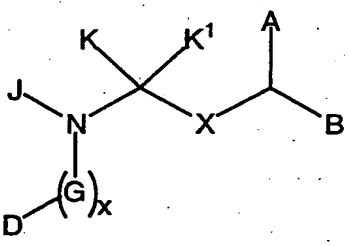
x is 0 or 1.

In another embodiment, the invention provides pharmaceutical compositions comprising the compounds of formula (I). These compositions may be utilized in methods treating various neurological diseases which are influenced by neuronal regeneration and axon growth or for stimulating neuronal regeneration in an *ex vivo* nerve cell. Examples of such diseases include peripheral nerve destruction due to physical injury or diseases such as diabetes; physical injuries to the central nervous system

(e.g., brain or spinal cord); stroke; neurological disturbances due to nerve degeneration, such as Parkinson's disease, Alzheimer's disease, and amylotrophic lateral sclerosis.

DETAILED DESCRIPTION OF THE INVENTION

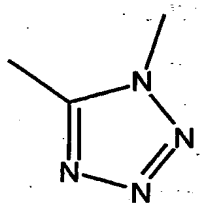
The invention provides compounds of formula (I):



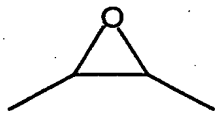
(I)

and pharmaceutically acceptable derivatives thereof, wherein:

X is selected from $-CH_2CH_2-$, $-CH=CH-$, $-C(OH)CH_2-$, $-CH_2C(OH)-$, $=C(F)CH_2-$, $-C(F)=CH_2-$, $-NHC(O)-$, $-P(O)(OH)CH_2-$, $-CH_2S(O)_2-$, $-C(S)NR^1-$, $-C(O)CH_2CH(OH)-$, $-C(OH)CF_2-$, $-C(O)CF_2-$, $-CH(F)CH_2-$, $-C(F)_2CH_2-$, $-CH_2CH(F)-$, $-CH_2C(F)_2-$,



or



A, B and R^1 are independently E, (C_1-C_{10})-straight or branched alkyl, (C_2-C_{10})-straight or branched alkenyl or alkynyl, or (C_5-C_7)-cycloalkyl or cycloalkenyl; wherein 1 or 2 hydrogen atoms in said alkyl, alkenyl or alkynyl are optionally and independently replaced with E, (C_5-C_7)-cycloalkyl or cycloalkenyl; and wherein 1 to 2 of the $-CH_2-$ groups in said alkyl, alkenyl, or alkynyl groups

is optionally and independently replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, =N-, -N= or $-N(R^3)-$;

or, B and R^1 are independently hydrogen;

R^3 is hydrogen, (C_1-C_4)-straight or branched alkyl, (C_3-C_4)-straight or branched alkenyl or alkynyl, or (C_1-C_4) bridging alkyl, wherein a bridge is formed between the nitrogen atom to which said R^3 is bound and any carbon atom of said alkyl, alkenyl or alkynyl to form a ring, and wherein said ring is optionally benzofused;

E is a saturated, partially saturated or unsaturated, or aromatic monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms independently selected from C, N, $N(R^3)$, O, S, S(O), or $S(O)_2$; and wherein no more than 4 ring atoms are selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$;

wherein 1 to 4 hydrogen atoms in E are optionally and independently replaced with halogen, hydroxyl, hydroxymethyl, nitro, SO_3H, trifluoromethyl, trifluoromethoxy, (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl, O-[(C_1-C_6)-straight or branched alkyl], O-[(C_3-C_6)-straight or branched alkenyl], $(CH_2)_n-N(R^4)(R^5)$, $(CH_2)_n-NH(R^4)-(CH_2)_n-Z$, $(CH_2)_n-N(R^4-(CH_2)_n-Z)(R^5-(CH_2)_n-Z)$, $(CH_2)_n-Z$, $O-(CH_2)_n-Z$, $(CH_2)_n-O-Z$, $S-(CH_2)_n-Z$, CH=CH-Z, 1,2-methylenedioxy, C(O)OH, C(O)O-[(C_1-C_6)-straight or branched alkyl], $C(O)O-(CH_2)_n-Z$ or $C(O)-N(R^4)(R^5)$;

each of R^4 and R^5 are independently hydrogen, (C_1-C_6)-straight or branched alkyl, (C_3-C_5)-straight or branched alkenyl, or wherein R^4 and R^5, when bound to the same nitrogen atom, are taken together with the nitrogen atom to form a 5 or 6 membered ring, wherein said ring

optionally contains 1 to 3 additional heteroatoms independently selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$; wherein said alkyl, alkenyl or alkynyl groups in R_4 and R_5 are optionally substituted with Z.

each n is independently 0 to 4;

each Z is independently selected from a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms independently selected from C, N, $N(R^3)$, O, S, S(O), or $S(O)_2$; and wherein no more than 4 ring atoms are selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$;

wherein 1 to 4 hydrogen atoms in Z are optionally and independently replaced with halo, hydroxy, nitro, cyano, C(O)OH, (C_1-C_3)-straight or branched alkyl, O-(C_1-C_3)-straight or branched alkyl, C(O)O-[(C_1-C_3)-straight or branched alkyl], amino, NH[(C_1-C_3)-straight or branched alkyl], or N-[(C_1-C_3)-straight or branched alkyl]$_2$;

J is H, methyl, ethyl or benzyl;

K and K^1 are independently selected from (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl or alkynyl, or cyclohexylmethyl, wherein 1 to 2 hydrogen atoms in said alkyl, alkenyl or alkynyl is optionally and independently replaced with E;

wherein K and K^1 are independently and optionally substituted with up to 3 substituents selected from halogen, OH, O-(C_1-C_6)-alkyl, O-(CH_2)n-Z, NO_2, C(O)OH, C(O)-O-(C_1-C_6)-alkyl, $C(O)NR^4R^5$, NR^4R^5 and $(CH_2)_n$-Z; or,

J and K, taken together with the nitrogen and carbon atom to which they are respectively bound, form a 5-7 membered heterocyclic ring, optionally containing up to 3

additional heteroatoms selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$, wherein 1 to 4 hydrogen atoms in said heterocyclic ring are optionally and independently replaced with (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl or alkynyl, oxo, hydroxyl or Z; and wherein any $-CH_2-$ group in said alkyl, alkenyl or alkynyl substituent is optionally and independently replaced by -O-, -S-, -S(O)-, $-S(O_2)-$, =N-, -N=, or $-N(R^3)-$; and wherein said heterocyclic ring is optionally fused with E;

G, when present, is $-S(O)_2-$, -C(O)-, $-S(O)_2-Y-$, -C(O)-Y-, -C(O)-C(O)-, or -C(O)-C(O)-Y-;

Y is oxygen, or $N(R^6)$;

wherein R^6 is hydrogen, E, (C_1-C_6)-straight or branched alkyl, (C_3-C_6)-straight or branched alkenyl or alkynyl; or wherein R^6 and D are taken together with the atoms to which they are bound to form a 5 to 7 membered ring system wherein said ring optionally contains 1 to 3 additional heteroatoms independently selected from O, S, N, $N(R^3)$, SO, or SO_2; and wherein said ring is optionally benzofused;

D is hydrogen, (C_1-C_7)-straight or branched alkyl, (C_2-C_7)-straight or branched alkenyl or alkynyl, (C_5-C_7)-cycloalkyl or cycloalkenyl optionally substituted with (C_1-C_6)-straight or branched alkyl or (C_2-C_7)-straight or branched alkenyl or alkynyl, $[(C_1-C_7)$-alkyl]-E, $[(C_2-C_7)$-alkenyl or alkynyl]-E, or E;

wherein 1 to 2 of the CH_2 groups of said alkyl, alkenyl or alkynyl chains in D is optionally replaced by -O-, -S-, -S(O)-, $-S(O_2)-$, =N-, -N=, or $-N(R^3)$;

provided that when J is hydrogen or G is selected from $-S(O)_2-$, $C(O)C(O)-$, SO_2-Y, $C(O)-Y$, or $C(O)C(O)-Y$, wherein Y is O; then D is not hydrogen; and

x is 0 or 1.

According to a preferred embodiment, each of A and B in formula (I) is (C_1-C_{10}) straight or branched alkyl, wherein 1-2 hydrogen atoms in said alkyl are optionally substituted with E.

In another preferred embodiment, B is hydrogen.

According to another preferred embodiment, each of A and B in formula (I) is $-CH_2-CH_2-E$ or $-CH_2-CH_2-CH_2-E$.

According to another preferred embodiment, D in formula (I) is (C_1-C_7) straight or branched alkyl, E or $[(C_1-C_6)$-straight or branched alkyl$]$-E.

According to a more preferred embodiment, D is an aromatic monocyclic or bicyclic ring system, wherein each ring comprises 5-7 ring atoms independently selected from C, N, O or S, and wherein no more than 4 ring atoms are selected from N, O or S.

According to an even more preferred embodiment, D is phenyl or C_1-C_7 straight or branched alkyl group.

According to another preferred embodiment, E in formula (I) is a monocyclic or bicyclic aromatic ring system, wherein said ring comprises 5-7 ring atoms independently selected from C, N, $N(R^3)$, O, S, S(O), or $S(O)_2$, and wherein 1 to 4 ring atoms are independently selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$.

Preferred embodiments of E include phenyl, napthyl, indenyl, azulenyl, fluorenyl, anthracenyl, furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl,

isothiazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, 1,3,5-trazinyl, 1,3,5-trithianyl, benzo[b]furanyl, benzo[b]thiophenyl, purinyl, cinnolinyl, phthalazinyl, isoxazolyl, triazolyl, oxadiazolyl, pyrimidinyl, pyrazinyl, indolinyl, indolizinyl, isoindolyl, benzimidazolyl, benzothiophenyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phnazinyl, phenothiazinyl, phenoxazinyl and benzothiazolyl, wherein E is optionally substituted as described above.

More preferred embodiments of E include phenyl, furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, triazolyl, oxadiazolyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzimidazolyl, benzothiophenyl, quinolinyl, isoquinolinyl, and benzothiazolyl, wherein E is optionally substituted as described above.

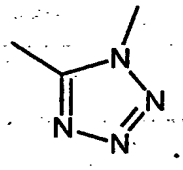
According to another preferred embodiment, J is H, methyl, ethyl or benzyl; and

K is selected from (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl or alkynyl, or cyclohexylmethyl, wherein 1 to 2 hydrogen atoms in said alkyl, alkenyl or alkynyl is optionally and independently replaced with E.

According to another preferred embodiment, J and K, taken together with the nitrogen atom, form a 5-7 membered heterocyclic ring, optionally containing up to 3 additional heteroatoms selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$, wherein 1 to 4 hydrogen atoms in said heterocyclic ring are optionally and independently

replaced with (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl or alkynyl, oxo, hydroxyl or Z; and wherein any $-CH_2-$ group said heterocyclic ring is optionally and independently replaced by -O-, -S-, -S(O)-, $-S(O_2)-$, =N-, -N=, or $-N(R^3)-$; and wherein said heterocyclic ring is optionally fused with E.

According to yet another preferred embodiment, X is selected from $-CH_2CH_2-$, -CH=CH-, $-C(OH)CH_2-$, $-CH_2C(OH)-$, $-C(F)=CH_2-$, $-CH_2S(O)_2-$, $-C(S)NR^1-$, $-C(O)CH_2CH(OH)-$, $-C(OH)CF_2-$, $-C(O)CF_2-$, $-CH(F)CH_2-$,



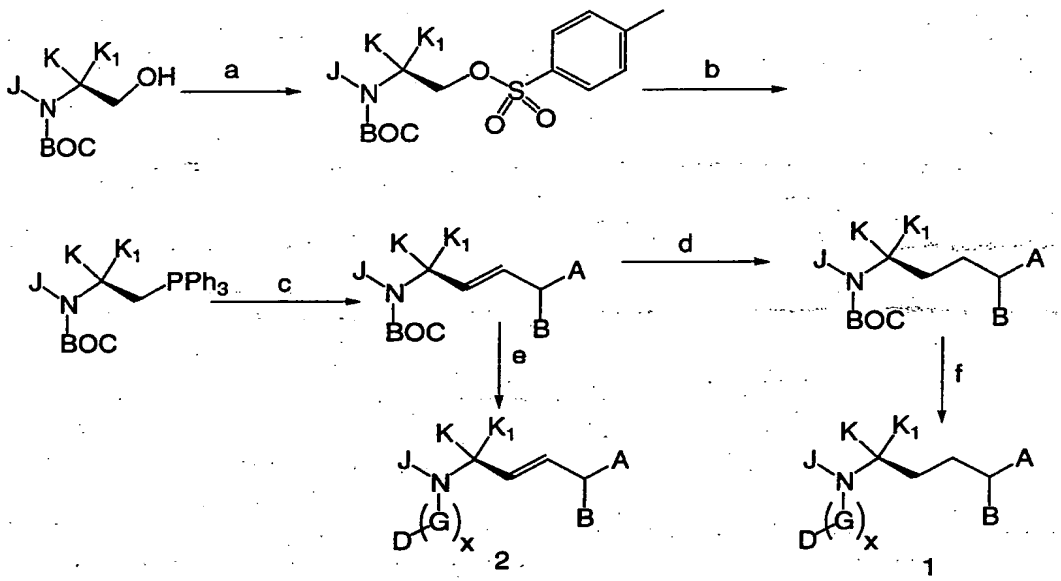
$-C(F)_2CH_2-$, $-CH_2CH(F)-$, $-CH_2C(F)_2-$, or .

The compounds of formula (I) may be stereoisomers, geometric isomers or stable tautomers. The invention envisions all possible isomers, such as E and Z isomers, S and R enantiomers, diastereoisomers, racemates, and mixtures of those. It is preferred that the substituent in the 2 position have the S configuration.

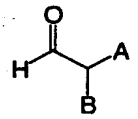
The compounds of the present invention may be readily prepared using known synthetic methods. For synthetic methods for the preparation of X, which are amide bond bioisosteres see: "Peptidomimetics Protocols" in Methods on Molecular Medicine, Vol 30, 1999, Humana Press, Totowa New Jersey, Kazmierski, W.M., Ed.

Examples of synthetic schemes that may be used to produce the compounds of this invention are set forth in Schemes 1 through 6 below.

Scheme 1

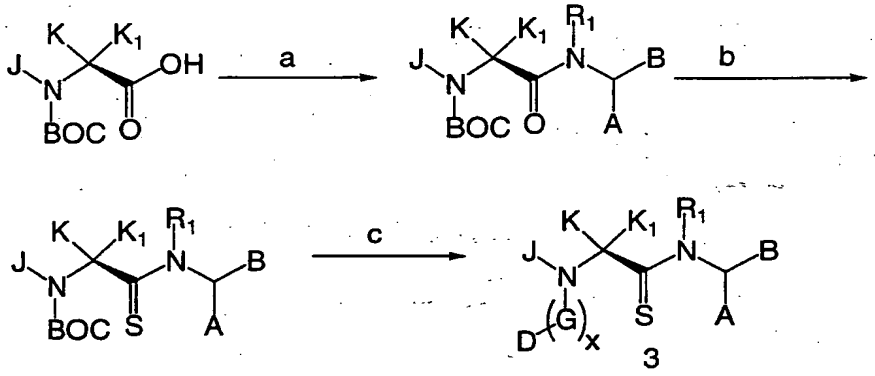


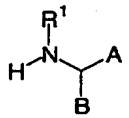
a = p-toluenesulfonyl chloride; diisopropylethylamine and CH_2Cl_2; b = NaI and acetone; followed by PPh3 and



toluene; c = NaH, and THF; followed by ; d = 10% Pd/C, H_2 gas, and MeOH; e = HCl(g)/ethyl acetate or TFA/dichloromethane; followed by $(CH_2)_x$-Br, K_2CO_3 and DMF if $(G)_x$ = $(CH_2)_x$; or D-C(O)-Cl, diisopropylethylamine, and CH_2Cl_2 if $(G)_x$ = -C(O), wherein X is 0 or 1.

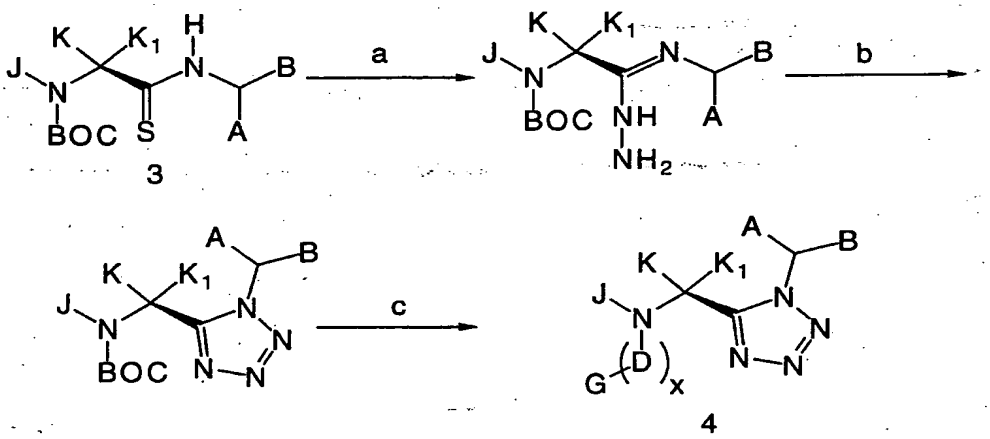
Scheme 2





a = , HOBT, EDC, and CH_2Cl_2; b = Lawesson's reagent and toluene; c = HCl(g)/ethyl acetate or TFA/dichloromethane; followed by $(CH_2)_x$-Br, K_2CO_3 and DMF if $(G)_x$ = $(CH_2)_x$; or D-C(O)-Cl, diisopropylethylamine, and CH_2Cl_2 if $(G)_x$ = -C(O), wherein X is 0 or 1. $(CH_2)_x$-Br, K_2CO_3 and DMF if $(G)_x$ = $(CH_2)_x$; or D-C(O)-Cl, diisopropylethylamine, and CH_2Cl_2 if $(G)_x$ = -C(O), wherein X is 0 or 1.

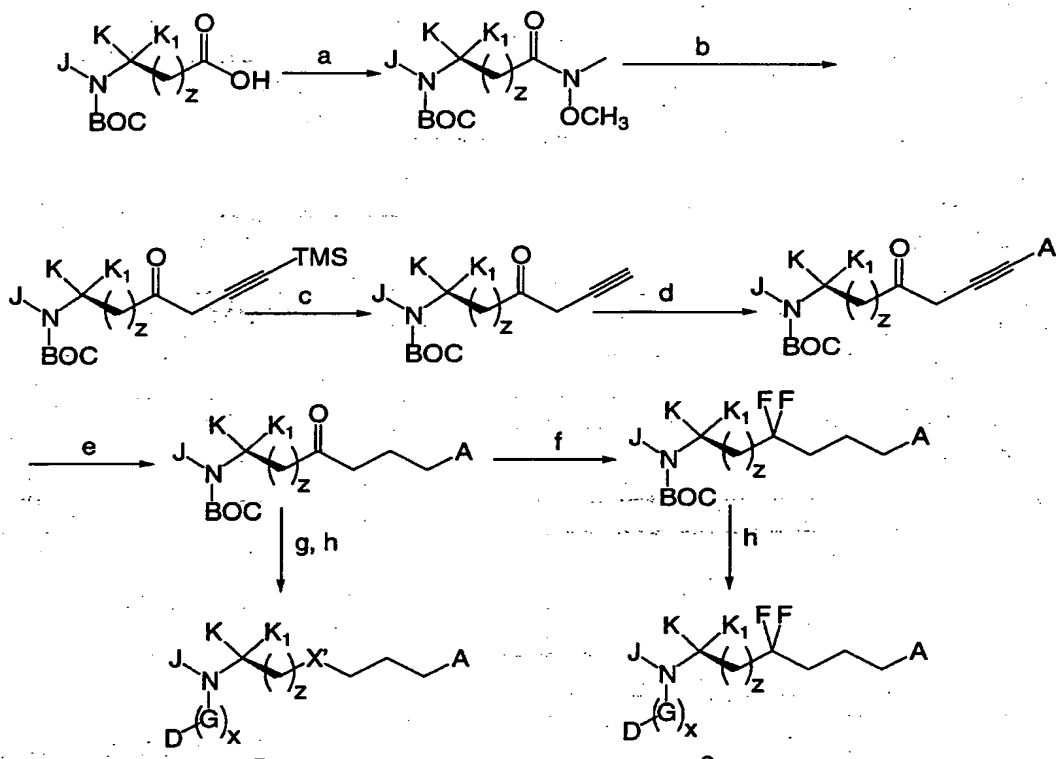
Scheme 3



a = $H_2NNH_2.H_2O$, and ethanol; b = $NaNO_2$, acetic acid, and H_2O; c = HCl(g)/ethyl acetate or TFA/dichloromethane; followed by $(CH_2)_x$-Br, K_2CO_3 and DMF if $(G)_x$ = $(CH_2)_x$; or D-

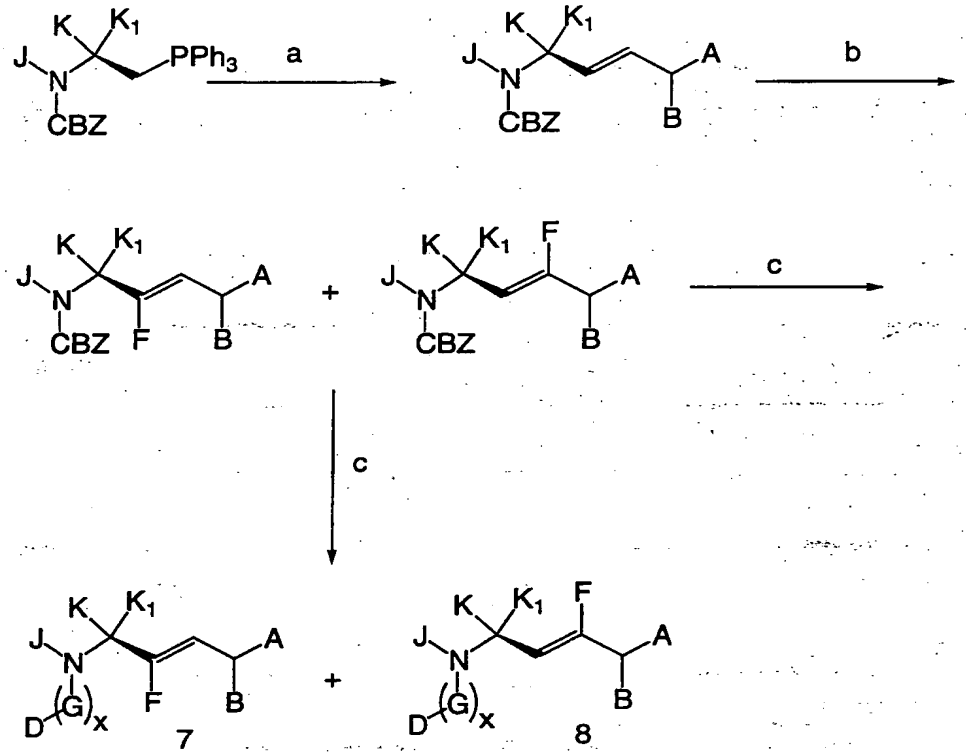
C(O)-Cl, diisopropylethylamine, and CH_2Cl_2 if $(G)_x$ = -C(O), wherein X is 0 or 1.

Scheme 4



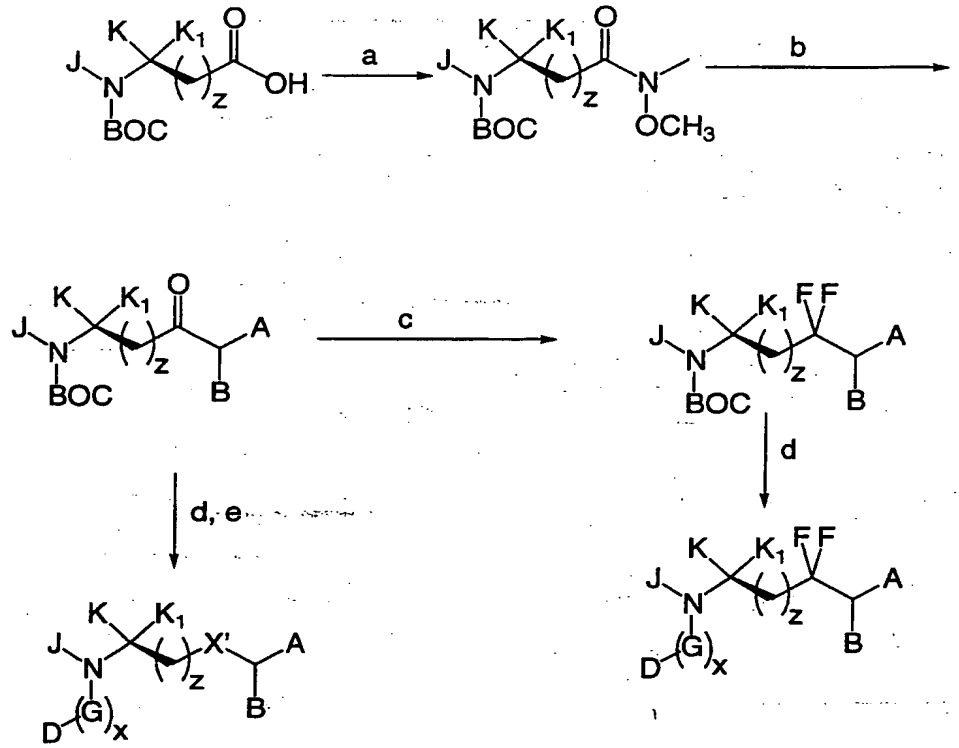
a = N,O-dimethylhydroxylamine hydrochloride, EDC, diisopropylethylamine, and CH_2Cl_2; b = 3-(trimethylsilyl)propargyl magnesium bromide and THF; c = Bu_4NF/THF; d = aryl halide (Br or I), $(Ph_3P)_4Pd(0)$, Et_3N, and THF; e = 5% Pd/C, H_2 (1 atm), and MeOH; f = Et_2N-SF_3, and CH_2Cl_2; g = $NaBH_4$, and MeOH, when X' = CH(OH) or DAST, and CH_2Cl_2, when X = CHF; h = HCl(g)/ethyl acetate or TFA/dichloromethane; followed by $(CH_2)_x$-Br, K_2CO_3 and DMF if $(G)_x$ = $(CH_2)_x$; or D-C(O)-Cl, diisopropylethylamine, and CH_2Cl_2 if $(G)_x$ = -C(O), wherein x is 0 or 1; z = 0 or 1; and X' = -C(O)-, -CH(OH)- or -CHF-.

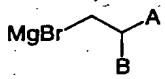
Scheme 5



a = NaH and THF; followed by aldehyde derivative; b = NBS, Bu_4NF/HF, and CH_2Cl_2; followed by KOtBu, and Et_2O; c = TMSI, and CH_3CN; followed by $(CH_2)_x$-Br, K_2CO_3 and DMF if $(G)_x$ = $(CH_2)_x$; or D-C(O)-Cl, diisopropylethylamine, and CH_2Cl_2 if $(G)_x$ = -C(O), wherein x is 0 or 1.

Scheme 6



a = N,O-dimethylhydroxylamine hydrochloride, EDC, diisopropylethylamine, and CH_2Cl_2; b =  and THF; c = Et_2N-SF_3, and CH_2Cl_2; d = $NaBH_4$, and MeOH, when X' = CH(OH), or DAST and CH_2Cl_2, when X = CHF; e = HCl(g)/ethyl acetate or TFA/dichloromethane; followed by $(CH_2)_x$-Br, K_2CO_3 and DMF if $(G)_x$ = $(CH_2)_x$; or D-C(O)-Cl, diisopropylethylamine, and CH_2Cl_2 if $(G)_x$ = -C(O), wherein x is 0 or 1; z = 0 or 1; and X' = -C(O)-, -CH(OH)- or -CHF-.

One of skill in the art will also be well aware of analogous synthetic methods for preparing compounds of formula (I).

According to another embodiment, this invention provides compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxy methylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

In another embodiment, the pharmaceutical composition of the present invention is comprised of a compound of formula (I), a pharmaceutically acceptable carrier, and a neurotrophic factor.

The term "neurotrophic factor," as used herein, refers to compounds which are capable of stimulating growth or proliferation of nervous tissue. Numerous neurotrophic factors have been identified in the art and any of those factors may be utilized in the compositions of this invention. These neurotrophic factors include, but are not limited to, nerve growth factor (NGF), insulin-like growth factor (IGF-1) and its active truncated derivatives such as gIGF-1 and Des(1-3)IGF-I, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary

neurotrophic factors (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3)and neurotrophin 4/5 (NT-4/5). The most preferred neurotrophic factor in the compositions of this invention is NGF.

As used herein, the described compounds used in the pharmaceutical compositions and methods of this invention, are defined to include pharmaceutically acceptable derivatives thereof. A "pharmaceutically acceptable derivative" denotes any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this invention or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to promote repair or prevent damage of neurons from disease or physical trauma.

If pharmaceutically acceptable salts of the described compounds are used, those salts are preferably derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate,

succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

The described compounds utilized in the compositions and methods of this invention may also be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous,

intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as Ph. Helv or similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In

the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment

containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

The amount of both a described compound and the optional neurotrophic factor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the described compound can be administered. If a neurotrophic factor is present in the composition, then a dosage of between 0.01 µg - 100 mg/kg body weight/day of the neurotrophic factor can be administered to a patient receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of active ingredients will also depend upon the particular described compound and neurotrophic factor in the composition.

According to another embodiment, this invention provides methods for promoting repair or preventing neuronal damage or neurodegeneration *in vivo* or in an *ex vivo* nerve cell. Such methods comprise the step of treating nerve cells with any of the compounds described above. Preferably, this method promotes repair or prevents neuronal damage or neurodegeneration in a patient, and the compound is formulated into a

composition additionally comprising a pharmaceutically acceptable carrier. The amount of the compound utilized in these methods is between about 0.01 and 100 mg/kg body weight/day.

According to an alternate embodiment, the method of promoting repair or preventing neuronal damage or neurodegeneration comprises the additional step of treating nerve cells with a neurotrophic factor, such as those contained in the pharmaceutical compositions of this invention. This embodiment includes administering the compound and the neurotrophic agent in a single dosage form or in separate, multiple dosage forms. If separate dosage forms are utilized, they may be administered concurrently, consecutively or within less than about 5 hours of one another.

Preferably, the methods of this invention are used to stimulate axonal growth in nerve cells. The compounds are, therefore, suitable for treating or preventing neuronal damage caused by a wide variety of diseases or physical traumas. These include, but are not limited to, Alzheimer's disease, Parkinson's disease, ALS, Huntington's disease, Tourette's syndrome, stroke and ischemia associated with stroke, neural paropathy, other neural degenerative diseases, motor neuron diseases, sciatic crush, spinal cord injuries and facial nerve crush.

In a particularly preferred embodiment of the invention, the method is used to treat a patient suffering from trigeminal neuralgia, glosspharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, muscle injury, progressive muscular atrophy,

progressive bulbar inherited muscular atrophy, herniated, ruptured, or prolapsed invertebrae disk syndrome's, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, such as those caused by lead, dapsone, ticks, or porphyria, other peripheral myelin disorders, Alzheimer's disease, Gullain-Barre syndrome, Parkinson's disease and other Parkinsonian disorders, ALS, Tourette's syndrome, multiple sclerosis, other central myelin disorders, stroke and ischemia associated with stroke, neural paropathy, other neural degenerative diseases, motor neuron diseases, sciatic crush, neuropathy associated with diabetes, spinal cord injuries, facial nerve crush and other trauma, chemotherapy- and other medication-induced neuropathies, and Huntington's disease.

More preferably, the compositions of the present invention are used for treating Parkinson's disease, amylotrophic lateral sclerosis, Alzheimer's disease, stroke, neuralgias, muscular atrophies, and Guillain-Barré syndrome.

For use of the compounds according to the invention as medications, they are administered in the form of a pharmaceutical preparation containing not only the active ingredient but also carriers, auxiliary substances, and/or additives suitable for enteric or parenteral administration. Administration can be oral or sublingual as a solid in the form of capsules or tablets, as a liquid in the form of solutions, suspensions, elixirs, aerosols or emulsions, or rectal in the form of suppositories, or in the form of solutions for injection

which can be given subcutaneously, intramuscularly, or intravenously, or which can be given topically or intrathecally. Auxiliary substances for the desired medicinal formulation include the inert organic and inorganic carriers known to those skilled in the art, such as water, gelatin, gum arabic, lactose, starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, etc. The medicinal formulations may also contain preservatives, stabilizers, wetting agents, emulsifiers, or salts to change the osmotic pressure or as buffers.

Solutions or suspensions for injection are suitable for parenteral administration, and especially aqueous solutions of the active compounds in polyhydroxy-ethoxylated castor oil.

Surface-active auxiliary substances such as salts of gallic acid, animal or vegetable phospholipids, or mixtures of them, and liposomes or their components, can be used as carrier systems.

The neurotrophic effect of the compounds of formula (I) of the present invention and their physiologically acceptable salts can be determined by the methods of W. E. Lyons et al., Proc. Natl. Acad. Sci. USA, Vol. 91, pp. 3191-3195 (1994) and W. E. Lyons et al., Proc. Natl. Acad. Sci. USA, Vol. 91, pages 3191-3195 (1994), the disclosures of which are herein incorporated by reference.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are

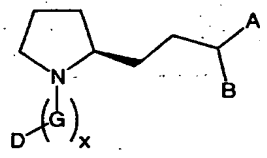
not to be construed as limiting the scope of the invention in any way.

EXAMPLE 1

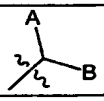
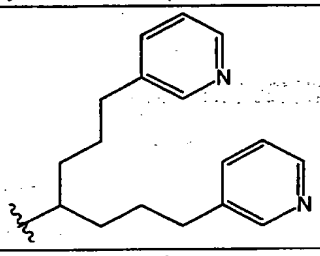
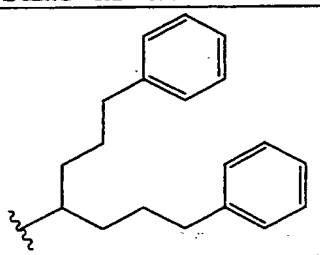
Compounds 100-295

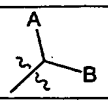
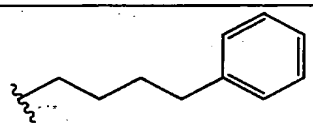
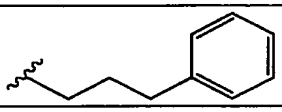
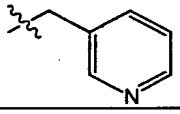
Compounds 101-296 are synthesized via the method set forth in Scheme 1, above. In all of the examples, "Ph" is phenyl.

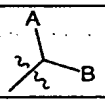
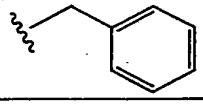
Compounds 100-148 have the formula:



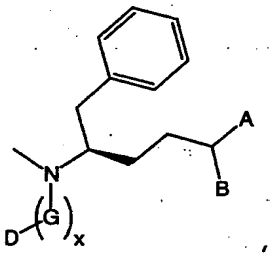
, with the individual variables defined in the table below.

Cmpd #		-(G)$_x$-D
100		$-CH_3$
101	Same as above	$-CH_2CH_3$
102	Same as above	$-C(=O)-CH_3$
103	Same as above	$-CH_2$-Ph
104	Same as above	$-C(=O)$-Ph
105	Same as above	$-C(=O)-O-CH_2$-Ph
106	Same as above	$-C(=O)-C(=O)$-Ph
107		$-CH_3$
108	Same as above	$-CH_2CH_3$

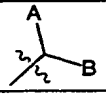
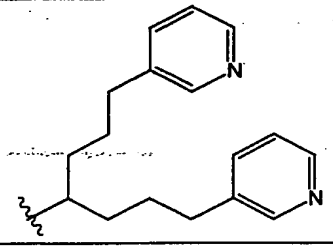
Cmpd #		-(G)$_x$-D
109	Same as above	-C(=O)-CH_3
110	Same as above	-CH_2-Ph
111	Same as above	-C(=O)-Ph
112	Same as above	-C(=O)-O-CH_2-Ph
113	Same as above	-C(=O)-C(=O)-Ph
114		-CH_3
115	Same as above	-CH_2CH_3
116	Same as above	-C(=O)-CH_3
117	Same as above	-CH_2-Ph
118	Same as above	-C(=O)-Ph
119	Same as above	-C(=O)-O-CH_2-Ph
120	Same as above	-C(=O)-C(=O)-Ph
121		-CH_3
122	Same as above	-CH_2CH_3
123	Same as above	-C(=O)-CH_3
124	Same as above	-CH_2-Ph
125	Same as above	-C(=O)-Ph
126	Same as above	-C(=O)-O-CH_2-Ph
127	Same as above	-C(=O)-C(=O)-Ph
128		-CH_3
129	Same as above	-CH_2CH_3
130	Same as above	-C(=O)-CH_3
131	Same as above	-CH_2-Ph
132	Same as above	-C(=O)-Ph
133	Same as above	-C(=O)-O-CH_2-Ph
134	Same as above	-C(=O)-C(=O)-Ph
135		-CH_3
136	Same as above	-CH_2CH_3
137	Same as above	-C(=O)-CH_3
138	Same as above	-CH_2-Ph
139	Same as above	-C(=O)-Ph
140	Same as above	-C(=O)-O-CH_2-Ph

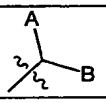
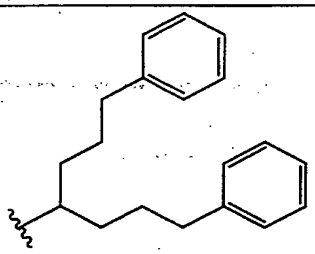
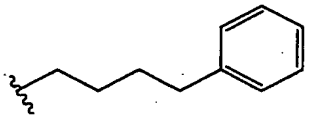
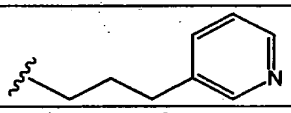
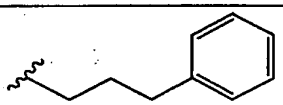
Cmpd #		$-(G)_x-D$
141	Same as above	$-C(=O)-C(=O)-Ph$
142		$-CH_3$
143	Same as above	$-CH_2CH_3$
144	Same as above	$-C(=O)-CH_3$
145	Same as above	$-CH_2-Ph$
146	Same as above	$-C(=O)-Ph$
147	Same as above	$-C(=O)-O-CH_2-Ph$
148	Same as above	$-C(=O)-C(=O)-Ph$

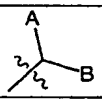
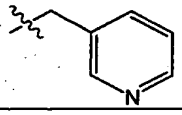
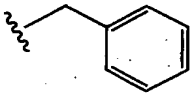
Compounds 149-197 have the formula:



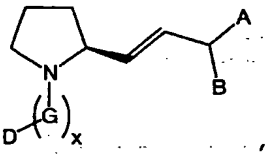
, with the individual variables defined in the table below.

Cmpd #		$-(G)_x-D$
149		$-CH_3$
150	Same as above	$-CH_2CH_3$
151	Same as above	$-C(=O)-CH_3$
152	Same as above	$-CH_2-Ph$
153	Same as above	$-C(=O)-Ph$
154	Same as above	$-C(=O)-O-CH_2-Ph$
155	Same as above	$-C(=O)-C(=O)-Ph$

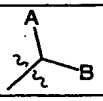
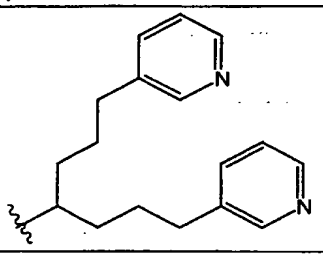
Cmpd #		-(G)$_x$-D
156		$-CH_3$
157	Same as above	$-CH_2CH_3$
158	Same as above	$-C(=O)-CH_3$
159	Same as above	$-CH_2$-Ph
160	Same as above	$-C(=O)$-Ph
161	Same as above	$-C(=O)-O-CH_2$-Ph
162	Same as above	$-C(=O)-C(=O)$-Ph
163		$-CH_3$
164	Same as above	$-CH_2CH_3$
165	Same as above	$-C(=O)-CH_3$
166	Same as above	$-CH_2$-Ph
167	Same as above	$-C(=O)$-Ph
168	Same as above	$-C(=O)-O-CH_2$-Ph
169	Same as above	$-C(=O)-C(=O)$-Ph
170		$-CH_3$
171	Same as above	$-CH_2CH_3$
172	Same as above	$-C(=O)-CH_3$
173	Same as above	$-CH_2$-Ph
174	Same as above	$-C(=O)$-Ph
175	Same as above	$-C(=O)-O-CH_2$-Ph
176	Same as above	$-C(=O)-C(=O)$-Ph
177		$-CH_3$
178	Same as above	$-CH_2CH_3$
179	Same as above	$-C(=O)-CH_3$
180	Same as above	$-CH_2$-Ph
181	Same as above	$-C(=O)$-Ph
182	Same as above	$-C(=O)-O-CH_2$-Ph
183	Same as above	$-C(=O)-C(=O)$-Ph

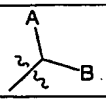
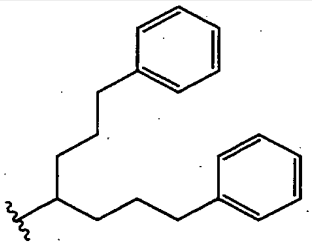
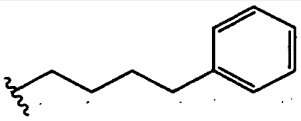
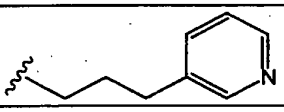
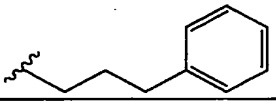
Cmpd #		$-(G)_x-D$
184		$-CH_3$
185	Same as above	$-CH_2CH_3$
186	Same as above	$-C(=O)-CH_3$
187	Same as above	$-CH_2-Ph$
188	Same as above	$-C(=O)-Ph$
189	Same as above	$-C(=O)-O-CH_2-Ph$
190	Same as above	$-C(=O)-C(=O)-Ph$
191		$-CH_3$
192	Same as above	$-CH_2CH_3$
193	Same as above	$-C(=O)-CH_3$
194	Same as above	$-CH_2-Ph$
195	Same as above	$-C(=O)-Ph$
196	Same as above	$-C(=O)-O-CH_2-Ph$
197	Same as above	$-C(=O)-C(=O)-Ph$

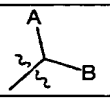
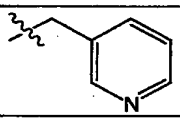
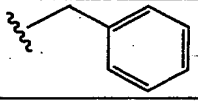
Compounds 198-246 have the formula:



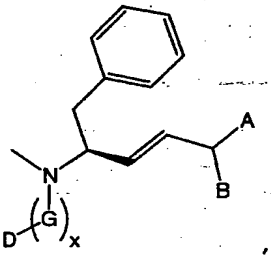
, with the individual variables defined in the table below.

Cmpd #		$-(G)_x-D$
198		$-CH_3$
199	Same as above	$-CH_2CH_3$
200	Same as above	$-C(=O)-CH_3$

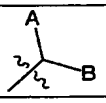
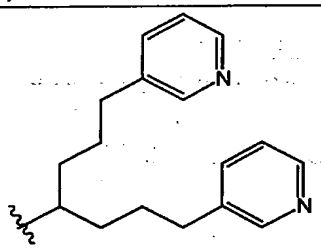
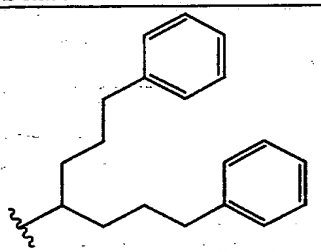
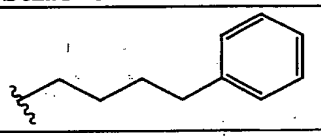
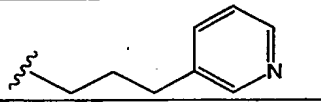
Cmpd #		-(G)$_x$-D
201	Same as above	-CH_2-Ph
202	Same as above	-C(=O)-Ph
203	Same as above	-C(=O)-O-CH_2-Ph
204	Same as above	-C(=O)-C(=O)-Ph
205		-CH_3
206	Same as above	-CH_2CH_3
207	Same as above	-C(=O)-CH_3
208	Same as above	-CH_2-Ph
209	Same as above	-C(=O)-Ph
210	Same as above	-C(=O)-O-CH_2-Ph
211	Same as above	-C(=O)-C(=O)-Ph
212		-CH_3
213	Same as above	-CH_2CH_3
214	Same as above	-C(=O)-CH_3
215	Same as above	-CH_2-Ph
216	Same as above	-C(=O)-Ph
217	Same as above	-C(=O)-O-CH_2-Ph
218	Same as above	-C(=O)-C(=O)-Ph
219		-CH_3
220	Same as above	-CH_2CH_3
221	Same as above	-C(=O)-CH_3
222	Same as above	-CH_2-Ph
223	Same as above	-C(=O)-Ph
224	Same as above	-C(=O)-O-CH_2-Ph
225	Same as above	-C(=O)-C(=O)-Ph
226		-CH_3
227	Same as above	-CH_2CH_3
228	Same as above	-C(=O)-CH_3

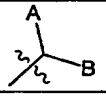
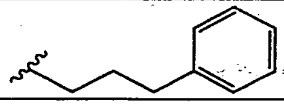
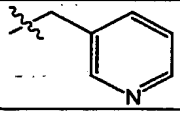
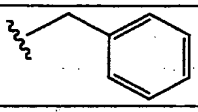
Cmpd #		-(G)$_x$-D
229	Same as above	-CH_2-Ph
230	Same as above	-C(=O)-Ph
231	Same as above	-C(=O)-O-CH_2-Ph
232	Same as above	-C(=O)-C(=O)-Ph
233		-CH_3
234	Same as above	-CH_2CH_3
235	Same as above	-C(=O)-CH_3
236	Same as above	-CH_2-Ph
237	Same as above	-C(=O)-Ph
238	Same as above	-C(=O)-O-CH_2-Ph
239	Same as above	-C(=O)-C(=O)-Ph
240		-CH_3
241	Same as above	-CH_2CH_3
242	Same as above	-C(=O)-CH_3
243	Same as above	-CH_2-Ph
244	Same as above	-C(=O)-Ph
245	Same as above	-C(=O)-O-CH_2-Ph
246	Same as above	-C(=O)-C(=O)-Ph

Compounds 247-295 have the formula:



, with the individual variables defined in the table below.

Cmpd #		-(G)$_x$-D
247		$-CH_3$
248	Same as above	$-CH_2CH_3$
249	Same as above	$-C(=O)-CH_3$
250	Same as above	$-CH_2$-Ph
251	Same as above	$-C(=O)$-Ph
252	Same as above	$-C(=O)-O-CH_2$-Ph
253	Same as above	$-C(=O)-C(=O)$-Ph
254		$-CH_3$
255	Same as above	$-CH_2CH_3$
256	Same as above	$-C(=O)-CH_3$
257	Same as above	$-CH_2$-Ph
258	Same as above	$-C(=O)$-Ph
259	Same as above	$-C(=O)-O-CH_2$-Ph
260	Same as above	$-C(=O)-C(=O)$-Ph
261		$-CH_3$
262	Same as above	$-CH_2CH_3$
263	Same as above	$-C(=O)-CH_3$
264	Same as above	$-CH_2$-Ph
265	Same as above	$-C(=O)$-Ph
266	Same as above	$-C(=O)-O-CH_2$-Ph
267	Same as above	$-C(=O)-C(=O)$-Ph
268		$-CH_3$

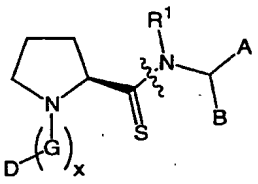
Cmpd #		-(G)$_x$-D
269	Same as above	$-CH_2CH_3$
270	Same as above	$-C(=O)-CH_3$
271	Same as above	$-CH_2$-Ph
272	Same as above	$-C(=O)$-Ph
273	Same as above	$-C(=O)-O-CH_2$-Ph
274	Same as above	$-C(=O)-C(=O)$-Ph
275		$-CH_3$
276	Same as above	$-CH_2CH_3$
277	Same as above	$-C(=O)-CH_3$
278	Same as above	$-CH_2$-Ph
279	Same as above	$-C(=O)$-Ph
280	Same as above	$-C(=O)-O-CH_2$-Ph
281	Same as above	$-C(=O)-C(=O)$-Ph
282		$-CH_3$
283	Same as above	$-CH_2CH_3$
284	Same as above	$-C(=O)-CH_3$
285	Same as above	$-CH_2$-Ph
286	Same as above	$-C(=O)$-Ph
287	Same as above	$-C(=O)-O-CH_2$-Ph
288	Same as above	$-C(=O)-C(=O)$-Ph
289		$-CH_3$
290	Same as above	$-CH_2CH_3$
291	Same as above	$-C(=O)-CH_3$
292	Same as above	$-CH_2$-Ph
293	Same as above	$-C(=O)$-Ph
294	Same as above	$-C(=O)-O-CH_2$-Ph
295	Same as above	$-C(=O)-C(=O)$-Ph

EXAMPLE 2

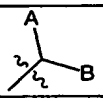
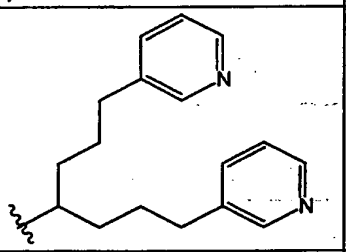
Compounds 296-519

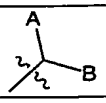
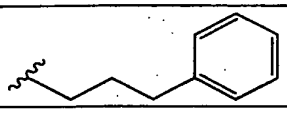
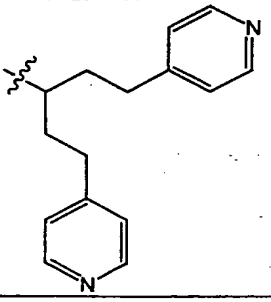
Compounds 296-519 are synthesized via the method set forth in Scheme 2, above.

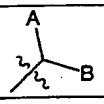
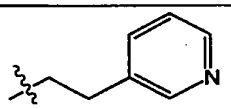
Compounds 296-407 have the formula:

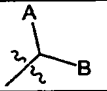


, with the individual variables defined in the table below.

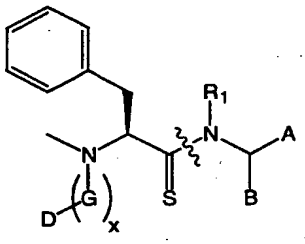
Cmpd #		R^1	$-(G)_x-D$
296		H	$-CH_3$
297	Same as above	H	$-CH_2CH_3$
298	Same as above	H	$-C(=O)-CH_3$
299	Same as above	H	$-CH_2$-Ph
300	Same as above	H	$-C(=O)$-Ph
301	Same as above	H	$-C(=O)-O-CH_2$-Ph
302	Same as above	H	$-C(=O)-C(=O)$-Ph
303	Same as above	CH_3	$-CH_3$
304	Same as above	CH_3	$-CH_2CH_3$
305	Same as above	CH_3	$-C(=O)-CH_3$
306	Same as above	CH_3	$-CH_2$-Ph
307	Same as above	CH_3	$-C(=O)$-Ph
308	Same as above	CH_3	$-C(=O)-O-CH_2$-Ph
309	Same as above	CH_3	$-C(=O)-C(=O)$-Ph
310	Same as above	CH_2CH_3	$-CH_3$
311	Same as above	CH_2CH_3	$-CH_2CH_3$
312	Same as above	CH_2CH_3	$-C(=O)-CH_3$
313	Same as above	CH_2CH_3	$-CH_2$-Ph
314	Same as above	CH_2CH_3	$-C(=O)$-Ph
315	Same as above	CH_2CH_3	$-C(=O)-O-CH_2$-Ph
316	Same as above	CH_2CH_3	$-C(=O)-C(=O)$-Ph
317	Same as above	CH_2Ph	$-CH_3$
318	Same as above	CH_2Ph	$-CH_2CH_3$
319	Same as above	CH_2Ph	$-C(=O)-CH_3$
320	Same as above	CH_2Ph	$-CH_2$-Ph
321	Same as above	CH_2Ph	$-C(=O)$-Ph

Cmpd #		R^1	$-(G)_x-D$
322	Same as above	CH_2Ph	$-C(=O)-O-CH_2-Ph$
323	Same as above	CH_2Ph	$-C(=O)-C(=O)-Ph$
324		H	$-CH_3$
325	Same as above	H	$-CH_2CH_3$
326	Same as above	H	$-C(=O)-CH_3$
327	Same as above	H	$-CH_2-Ph$
328	Same as above	H	$-C(=O)-Ph$
329	Same as above	H	$-C(=O)-O-CH_2-Ph$
330	Same as above	H	$-C(=O)-C(=O)-Ph$
331	Same as above	CH_3	$-CH_3$
332	Same as above	CH_3	$-CH_2CH_3$
333	Same as above	CH_3	$-C(=O)-CH_3$
334	Same as above	CH_3	$-CH_2-Ph$
335	Same as above	CH_3	$-C(=O)-Ph$
336	Same as above	CH_3	$-C(=O)-O-CH_2-Ph$
337	Same as above	CH_3	$-C(=O)-C(=O)-Ph$
338	Same as above	CH_2CH_3	$-CH_3$
339	Same as above	CH_2CH_3	$-CH_2CH_3$
340	Same as above	CH_2CH_3	$-C(=O)-CH_3$
341	Same as above	CH_2CH_3	$-CH_2-Ph$
342	Same as above	CH_2CH_3	$-C(=O)-Ph$
343	Same as above	CH_2CH_3	$-C(=O)-O-CH_2-Ph$
344	Same as above	CH_2CH_3	$-C(=O)-C(=O)-Ph$
345	Same as above	CH_2Ph	$-CH_3$
346	Same as above	CH_2Ph	$-CH_2CH_3$
347	Same as above	CH_2Ph	$-C(=O)-CH_3$
348	Same as above	CH_2Ph	$-CH_2-Ph$
349	Same as above	CH_2Ph	$-C(=O)-Ph$
350	Same as above	CH_2Ph	$-C(=O)-O-CH_2-Ph$
351	Same as above	CH_2Ph	$-C(=O)-C(=O)-Ph$
352		H	$-CH_3$
353	Same as above	H	$-CH_2CH_3$

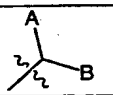
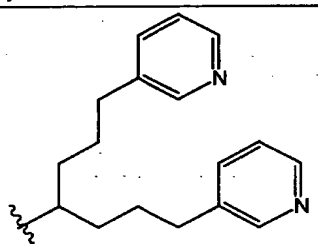
Cmpd #		R^1	$-(G)_x-D$
354	Same as above	H	$-C(=O)-CH_3$
355	Same as above	H	$-CH_2-Ph$
356	Same as above	H	$-C(=O)-Ph$
357	Same as above	H	$-C(=O)-O-CH_2-Ph$
358	Same as above	H	$-C(=O)-C(=O)-Ph$
359	Same as above	CH_3	$-CH_3$
360	Same as above	CH_3	$-CH_2CH_3$
361	Same as above	CH_3	$-C(=O)-CH_3$
362	Same as above	CH_3	$-CH_2-Ph$
363	Same as above	CH_3	$-C(=O)-Ph$
364	Same as above	CH_3	$-C(=O)-O-CH_2-Ph$
365	Same as above	CH_3	$-C(=O)-C(=O)-Ph$
366	Same as above	CH_2CH_3	$-CH_3$
367	Same as above	CH_2CH_3	$-CH_2CH_3$
368	Same as above	CH_2CH_3	$-C(=O)-CH_3$
369	Same as above	CH_2CH_3	$-CH_2-Ph$
370	Same as above	CH_2CH_3	$-C(=O)-Ph$
371	Same as above	CH_2CH_3	$-C(=O)-O-CH_2-Ph$
372	Same as above	CH_2CH_3	$-C(=O)-C(=O)-Ph$
373	Same as above	CH_2Ph	$-CH_3$
374	Same as above	CH_2Ph	$-CH_2CH_3$
375	Same as above	CH_2Ph	$-C(=O)-CH_3$
376	Same as above	CH_2Ph	$-CH_2-Ph$
377	Same as above	CH_2Ph	$-C(=O)-Ph$
378	Same as above	CH_2Ph	$-C(=O)-O-CH_2-Ph$
379	Same as above	CH_2Ph	$-C(=O)-C(=O)-Ph$
380		H	$-CH_3$
381	Same as above	H	$-CH_2CH_3$
382	Same as above	H	$-C(=O)-CH_3$
383	Same as above	H	$-CH_2-Ph$
384	Same as above	H	$-C(=O)-Ph$
385	Same as above	H	$-C(=O)-O-CH_2-Ph$
386	Same as above	H	$-C(=O)-C(=O)-Ph$
387	Same as above	CH_3	$-CH_3$
388	Same as above	CH_3	$-CH_2CH_3$
389	Same as above	CH_3	$-C(=O)-CH_3$
390	Same as above	CH_3	$-CH_2-Ph$
391	Same as above	CH_3	$-C(=O)-Ph$
392	Same as above	CH_3	$-C(=O)-O-CH_2-Ph$
393	Same as above	CH_3	$-C(=O)-C(=O)-Ph$

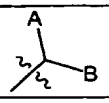
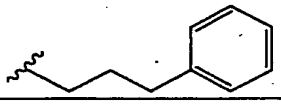
Cmpd #		R^1	$-(G)_x-D$
394	Same as above	CH_2CH_3	$-CH_3$
395	Same as above	CH_2CH_3	$-CH_2CH_3$
396	Same as above	CH_2CH_3	$-C(=O)-CH_3$
397	Same as above	CH_2CH_3	$-CH_2-Ph$
398	Same as above	CH_2CH_3	$-C(=O)-Ph$
399	Same as above	CH_2CH_3	$-C(=O)-O-CH_2-Ph$
400	Same as above	CH_2CH_3	$-C(=O)-C(=O)-Ph$
401	Same as above	CH_2Ph	$-CH_3$
402	Same as above	CH_2Ph	$-CH_2CH_3$
403	Same as above	CH_2Ph	$-C(=O)-CH_3$
404	Same as above	CH_2Ph	$-CH_2-Ph$
405	Same as above	CH_2Ph	$-C(=O)-Ph$
406	Same as above	CH_2Ph	$-C(=O)-O-CH_2-Ph$
407	Same as above	CH_2Ph	$-C(=O)-C(=O)-Ph$

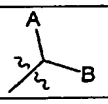
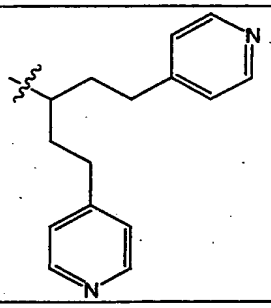
Compounds 408-519 have the formula:

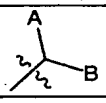
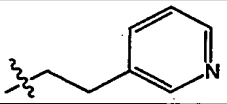


, with the individual variables defined in the table below.

Cmpd #		R^1	$-(G)_x-D$
408		H	$-CH_3$
409	Same as above	H	$-CH_2CH_3$
410	Same as above	H	$-C(=O)-CH_3$
411	Same as above	H	$-CH_2-Ph$
412	Same as above	H	$-C(=O)-Ph$
413	Same as above	H	$-C(=O)-O-CH_2-Ph$

Cmpd #		R^1	$-(G)_x-D$
414	Same as above	H	$-C(=O)-C(=O)-Ph$
415	Same as above	CH_3	$-CH_3$
416	Same as above	CH_3	$-CH_2CH_3$
417	Same as above	CH_3	$-C(=O)-CH_3$
418	Same as above	CH_3	$-CH_2-Ph$
419	Same as above	CH_3	$-C(=O)-Ph$
420	Same as above	CH_3	$-C(=O)-O-CH_2-Ph$
421	Same as above	CH_3	$-C(=O)-C(=O)-Ph$
422	Same as above	CH_2CH_3	$-CH_3$
423	Same as above	CH_2CH_3	$-CH_2CH_3$
424	Same as above	CH_2CH_3	$-C(=O)-CH_3$
425	Same as above	CH_2CH_3	$-CH_2-Ph$
426	Same as above	CH_2CH_3	$-C(=O)-Ph$
427	Same as above	CH_2CH_3	$-C(=O)-O-CH_2-Ph$
428	Same as above	CH_2CH_3	$-C(=O)-C(=O)-Ph$
429	Same as above	CH_2Ph	$-CH_3$
430	Same as above	CH_2Ph	$-CH_2CH_3$
431	Same as above	CH_2Ph	$-C(=O)-CH_3$
432	Same as above	CH_2Ph	$-CH_2-Ph$
433	Same as above	CH_2Ph	$-C(=O)-Ph$
434	Same as above	CH_2Ph	$-C(=O)-O-CH_2-Ph$
435	Same as above	CH_2Ph	$-C(=O)-C(=O)-Ph$
436		H	$-CH_3$
437	Same as above	H	$-CH_2CH_3$
438	Same as above	H	$-C(=O)-CH_3$
439	Same as above	H	$-CH_2-Ph$
440	Same as above	H	$-C(=O)-Ph$
441	Same as above	H	$-C(=O)-O-CH_2-Ph$
442	Same as above	H	$-C(=O)-C(=O)-Ph$
443	Same as above	CH_3	$-CH_3$
444	Same as above	CH_3	$-CH_2CH_3$
445	Same as above	CH_3	$-C(=O)-CH_3$
446	Same as above	CH_3	$-CH_2-Ph$
447	Same as above	CH_3	$-C(=O)-Ph$
448	Same as above	CH_3	$-C(=O)-O-CH_2-Ph$
449	Same as above	CH_3	$-C(=O)-C(=O)-Ph$
450	Same as above	CH_2CH_3	$-CH_3$
451	Same as above	CH_2CH_3	$-CH_2CH_3$
452	Same as above	CH_2CH_3	$-C(=O)-CH_3$
453	Same as above	CH_2CH_3	$-CH_2-Ph$

Cmpd #		R^1	$-(G)_x-D$
454	Same as above	CH_2CH_3	$-C(=O)-Ph$
455	Same as above	CH_2CH_3	$-C(=O)-O-CH_2-Ph$
456	Same as above	CH_2CH_3	$-C(=O)-C(=O)-Ph$
457	Same as above	CH_2Ph	$-CH_3$
458	Same as above	CH_2Ph	$-CH_2CH_3$
459	Same as above	CH_2Ph	$-C(=O)-CH_3$
460	Same as above	CH_2Ph	$-CH_2-Ph$
461	Same as above	CH_2Ph	$-C(=O)-Ph$
462	Same as above	CH_2Ph	$-C(=O)-O-CH_2-Ph$
463	Same as above	CH_2Ph	$-C(=O)-C(=O)-Ph$
464		H	$-CH_3$
465	Same as above	H	$-CH_2CH_3$
466	Same as above	H	$-C(=O)-CH_3$
467	Same as above	H	$-CH_2-Ph$
468	Same as above	H	$-C(=O)-Ph$
469	Same as above	H	$-C(=O)-O-CH_2-Ph$
470	Same as above	H	$-C(=O)-C(=O)-Ph$
471	Same as above	CH_3	$-CH_3$
472	Same as above	CH_3	$-CH_2CH_3$
473	Same as above	CH_3	$-C(=O)-CH_3$
474	Same as above	CH_3	$-CH_2-Ph$
475	Same as above	CH_3	$-C(=O)-Ph$
476	Same as above	CH_3	$-C(=O)-O-CH_2-Ph$
477	Same as above	CH_3	$-C(=O)-C(=O)-Ph$
478	Same as above	CH_2CH_3	$-CH_3$
479	Same as above	CH_2CH_3	$-CH_2CH_3$
480	Same as above	CH_2CH_3	$-C(=O)-CH_3$
481	Same as above	CH_2CH_3	$-CH_2-Ph$
482	Same as above	CH_2CH_3	$-C(=O)-Ph$
483	Same as above	CH_2CH_3	$-C(=O)-O-CH_2-Ph$
484	Same as above	CH_2CH_3	$-C(=O)-C(=O)-Ph$
485	Same as above	CH_2Ph	$-CH_3$
486	Same as above	CH_2Ph	$-CH_2CH_3$
487	Same as above	CH_2Ph	$-C(=O)-CH_3$

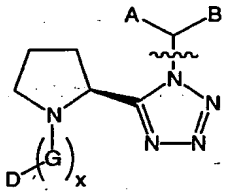
Cmpd #		R^1	$-(G)_x-D$
488	Same as above	CH_2Ph	$-CH_2-Ph$
489	Same as above	CH_2Ph	$-C(=O)-Ph$
490	Same as above	CH_2Ph	$-C(=O)-O-CH_2-Ph$
491	Same as above	CH_2Ph	$-C(=O)-C(=O)-Ph$
492		H	$-CH_3$
493	Same as above	H	$-CH_2CH_3$
494	Same as above	H	$-C(=O)-CH_3$
495	Same as above	H	$-CH_2-Ph$
496	Same as above	H	$-C(=O)-Ph$
497	Same as above	H	$-C(=O)-O-CH_2-Ph$
498	Same as above	H	$-C(=O)-C(=O)-Ph$
499	Same as above	CH_3	$-CH_3$
500	Same as above	CH_3	$-CH_2CH_3$
501	Same as above	CH_3	$-C(=O)-CH_3$
502	Same as above	CH_3	$-CH_2-Ph$
503	Same as above	CH_3	$-C(=O)-Ph$
504	Same as above	CH_3	$-C(=O)-O-CH_2-Ph$
505	Same as above	CH_3	$-C(=O)-C(=O)-Ph$
506	Same as above	CH_2CH_3	$-CH_3$
507	Same as above	CH_2CH_3	$-CH_2CH_3$
508	Same as above	CH_2CH_3	$-C(=O)-CH_3$
509	Same as above	CH_2CH_3	$-CH_2-Ph$
510	Same as above	CH_2CH_3	$-C(=O)-Ph$
511	Same as above	CH_2CH_3	$-C(=O)-O-CH_2-Ph$
512	Same as above	CH_2CH_3	$-C(=O)-C(=O)-Ph$
513	Same as above	CH_2Ph	$-CH_3$
514	Same as above	CH_2Ph	$-CH_2CH_3$
515	Same as above	CH_2Ph	$-C(=O)-CH_3$
516	Same as above	CH_2Ph	$-CH_2-Ph$
517	Same as above	CH_2Ph	$-C(=O)-Ph$
518	Same as above	CH_2Ph	$-C(=O)-O-CH_2-Ph$
519	Same as above	CH_2Ph	$-C(=O)-C(=O)-Ph$

EXAMPLE 3

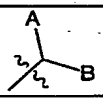
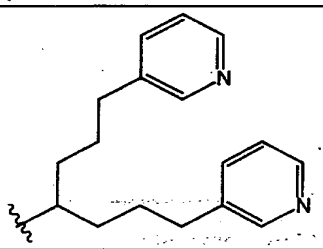
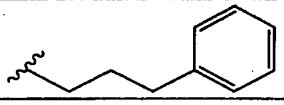
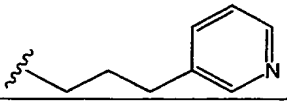
Compounds 520-561

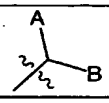
Compounds 520-561 are synthesized via the method set forth in Scheme 3, above.

Compounds 520-540 have the formula:

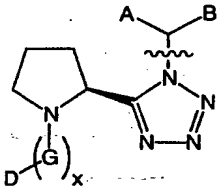


, with the individual variables defined in the table below.

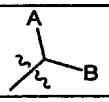
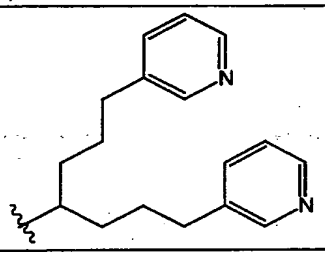
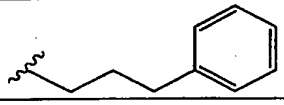
Cmpd #		$-(G)_x-D$
520		$-CH_3$
521	Same as above	$-CH_2CH_3$
522	Same as above	$-C(=O)-CH_3$
523	Same as above	$-CH_2$-Ph
524	Same as above	$-C(=O)$-Ph
525	Same as above	$-C(=O)-O-CH_2$-Ph
526	Same as above	$-C(=O)-C(=O)$-Ph
527		$-CH_3$
528	Same as above	$-CH_2CH_3$
529	Same as above	$-C(=O)-CH_3$
530	Same as above	$-CH_2$-Ph
531	Same as above	$-C(=O)$-Ph
532	Same as above	$-C(=O)-O-CH_2$-Ph
533	Same as above	$-C(=O)-C(=O)$-Ph
534		$-CH_3$

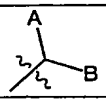
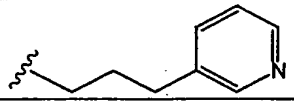
Cmpd #		-(G)$_x$-D
535	Same as above	-CH_2CH_3
536	Same as above	-C(=O)-CH_3
537	Same as above	-CH_2-Ph
538	Same as above	-C(=O)-Ph
539	Same as above	-C(=O)-O-CH_2-Ph
540	Same as above	-C(=O)-C(=O)-Ph

Compounds 541-561 have the formula:



, with the individual variables defined in the table below.

Cmpd #		-(G)$_x$-D
541		-CH_3
542	Same as above	-CH_2CH_3
543	Same as above	-C(=O)-CH_3
544	Same as above	-CH_2-Ph
545	Same as above	-C(=O)-Ph
546	Same as above	-C(=O)-O-CH_2-Ph
547	Same as above	-C(=O)-C(=O)-Ph
548		-CH_3
549	Same as above	-CH_2CH_3
550	Same as above	-C(=O)-CH_3
551	Same as above	-CH_2-Ph
552	Same as above	-C(=O)-Ph
553	Same as above	-C(=O)-O-CH_2-Ph

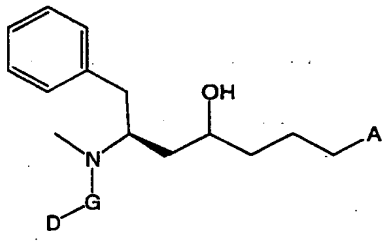
Cmpd #		$-(G)_x-D$
554	Same as above	$-C(=O)-C(=O)-Ph$
555		$-CH_3$
556	Same as above	$-CH_2CH_3$
557	Same as above	$-C(=O)-CH_3$
558	Same as above	$-CH_2-Ph$
559	Same as above	$-C(=O)-Ph$
560	Same as above	$-C(=O)-O-CH_2-Ph$
561	Same as above	$-C(=O)-C(=O)-Ph$

EXAMPLE 4

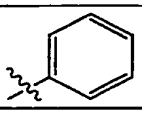
Compounds 562-771

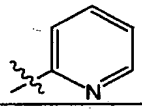
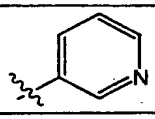
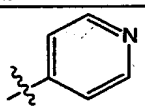
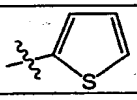
Compounds 562-771 are synthesized via the method set forth in Scheme 4 or Scheme 6, above.

Compounds 562-596 have the formula:

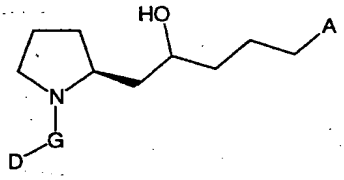


, with the individual variables defined in the table below.

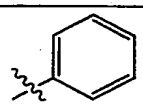
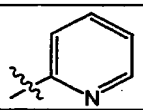
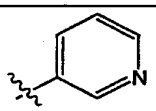
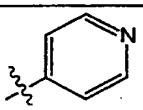
Cmpd #	A	$-(G)_x-D$
562		$-CH_3$
563	Same as above	$-CH_2CH_3$
564	Same as above	$-C(=O)-CH_3$
565	Same as above	$-CH_2-Ph$
566	Same as above	$-C(=O)-Ph$
567	Same as above	$-C(=O)-O-CH_2-Ph$
568	Same as above	$-C(=O)-C(=O)-Ph$

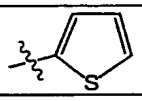
Cmpd #	A	-(G)$_x$-D
569		$-CH_3$
570	Same as above	$-CH_2CH_3$
571	Same as above	$-C(=O)-CH_3$
572	Same as above	$-CH_2$-Ph
573	Same as above	$-C(=O)$-Ph
574	Same as above	$-C(=O)-O-CH_2$-Ph
575	Same as above	$-C(=O)-C(=O)$-Ph
576		$-CH_3$
577	Same as above	$-CH_2CH_3$
578	Same as above	$-C(=O)-CH_3$
579	Same as above	$-CH_2$-Ph
580	Same as above	$-C(=O)$-Ph
581	Same as above	$-C(=O)-O-CH_2$-Ph
582	Same as above	$-C(=O)-C(=O)$-Ph
583		$-CH_3$
584	Same as above	$-CH_2CH_3$
585	Same as above	$-C(=O)-CH_3$
586	Same as above	$-CH_2$-Ph
587	Same as above	$-C(=O)$-Ph
588	Same as above	$-C(=O)-O-CH_2$-Ph
589	Same as above	$-C(=O)-C(=O)$-Ph
590		$-CH_3$
591	Same as above	$-CH_2CH_3$
592	Same as above	$-C(=O)-CH_3$
593	Same as above	$-CH_2$-Ph
594	Same as above	$-C(=O)$-Ph
595	Same as above	$-C(=O)-O-CH_2$-Ph
596	Same as above	$-C(=O)-C(=O)$-Ph

Compounds 597-631 have the formula:

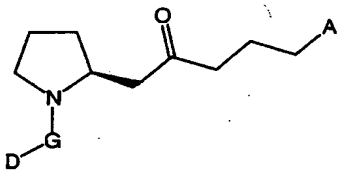


, with the individual variables defined in the table below.

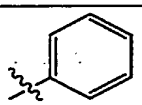
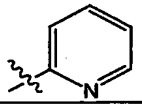
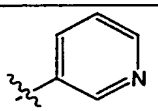
Cmpd #	A	$-(G)_x-D$
597		$-CH_3$
598	Same as above	$-CH_2CH_3$
599	Same as above	$-C(=O)-CH_3$
600	Same as above	$-CH_2-Ph$
601	Same as above	$-C(=O)-Ph$
602	Same as above	$-C(=O)-O-CH_2-Ph$
603	Same as above	$-C(=O)-C(=O)-Ph$
604		$-CH_3$
605	Same as above	$-CH_2CH_3$
606	Same as above	$-C(=O)-CH_3$
607	Same as above	$-CH_2-Ph$
608	Same as above	$-C(=O)-Ph$
609	Same as above	$-C(=O)-O-CH_2-Ph$
610	Same as above	$-C(=O)-C(=O)-Ph$
611		$-CH_3$
612	Same as above	$-CH_2CH_3$
613	Same as above	$-C(=O)-CH_3$
614	Same as above	$-CH_2-Ph$
615	Same as above	$-C(=O)-Ph$
616	Same as above	$-C(=O)-O-CH_2-Ph$
617	Same as above	$-C(=O)-C(=O)-Ph$
618		$-CH_3$
619	Same as above	$-CH_2CH_3$
620	Same as above	$-C(=O)-CH_3$
621	Same as above	$-CH_2-Ph$
622	Same as above	$-C(=O)-Ph$

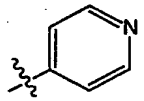
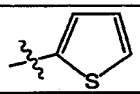
Cmpd #	A	$-(G)_x-D$
623	Same as above	$-C(=O)-O-CH_2-Ph$
624	Same as above	$-C(=O)-C(=O)-Ph$
625		$-CH_3$
626	Same as above	$-CH_2CH_3$
627	Same as above	$-C(=O)-CH_3$
628	Same as above	$-CH_2-Ph$
629	Same as above	$-C(=O)-Ph$
630	Same as above	$-C(=O)-O-CH_2-Ph$
631	Same as above	$-C(=O)-C(=O)-Ph$

Compounds 632-666 have the formula:

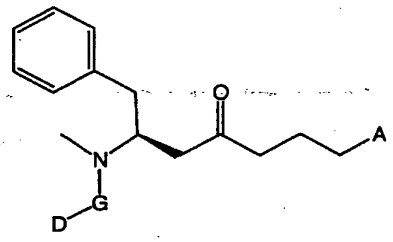


, with the individual variables defined in the table below.

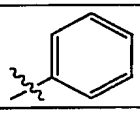
Cmpd #	A	$-(G)_x-D$
632		$-CH_3$
633	Same as above	$-CH_2CH_3$
634	Same as above	$-C(=O)-CH_3$
635	Same as above	$-CH_2-Ph$
636	Same as above	$-C(=O)-Ph$
637	Same as above	$-C(=O)-O-CH_2-Ph$
638	Same as above	$-C(=O)-C(=O)-Ph$
639		$-CH_3$
640	Same as above	$-CH_2CH_3$
641	Same as above	$-C(=O)-CH_3$
642	Same as above	$-CH_2-Ph$
643	Same as above	$-C(=O)-Ph$
644	Same as above	$-C(=O)-O-CH_2-Ph$
645	Same as above	$-C(=O)-C(=O)-Ph$
646		$-CH_3$

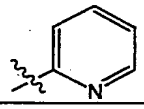
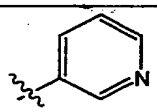
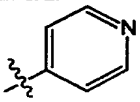
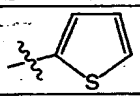
Cmpd #	A	-(G)$_x$-D
647	Same as above	$-CH_2CH_3$
648	Same as above	$-C(=O)-CH_3$
649	Same as above	$-CH_2$-Ph
650	Same as above	$-C(=O)$-Ph
651	Same as above	$-C(=O)-O-CH_2$-Ph
652	Same as above	$-C(=O)-C(=O)$-Ph
653		$-CH_3$
654	Same as above	$-CH_2CH_3$
655	Same as above	$-C(=O)-CH_3$
656	Same as above	$-CH_2$-Ph
657	Same as above	$-C(=O)$-Ph
658	Same as above	$-C(=O)-O-CH_2$-Ph
659	Same as above	$-C(=O)-C(=O)$-Ph
660		$-CH_3$
661	Same as above	$-CH_2CH_3$
662	Same as above	$-C(=O)-CH_3$
663	Same as above	$-CH_2$-Ph
664	Same as above	$-C(=O)$-Ph
665	Same as above	$-C(=O)-O-CH_2$-Ph
666	Same as above	$-C(=O)-C(=O)$-Ph

Compounds 667-701 have the formula:

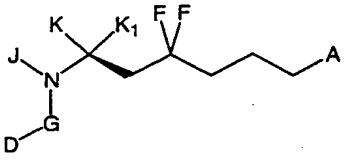


, with the individual variables defined in the table below.

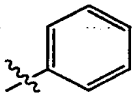
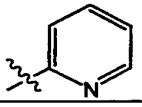
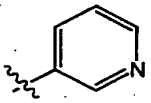
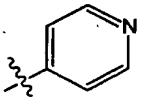
Cmpd #	A	-(G)$_x$-D
667		$-CH_3$
668	Same as above	$-CH_2CH_3$
669	Same as above	$-C(=O)-CH_3$
670	Same as above	$-CH_2$-Ph

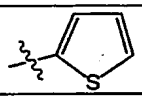
Cmpd #	A	$-(G)_x-D$
671	Same as above	$-C(=O)-Ph$
672	Same as above	$-C(=O)-O-CH_2-Ph$
673	Same as above	$-C(=O)-C(=O)-Ph$
674		$-CH_3$
675	Same as above	$-CH_2CH_3$
676	Same as above	$-C(=O)-CH_3$
677	Same as above	$-CH_2-Ph$
678	Same as above	$-C(=O)-Ph$
679	Same as above	$-C(=O)-O-CH_2-Ph$
680	Same as above	$-C(=O)-C(=O)-Ph$
681		$-CH_3$
682	Same as above	$-CH_2CH_3$
683	Same as above	$-C(=O)-CH_3$
684	Same as above	$-CH_2-Ph$
685	Same as above	$-C(=O)-Ph$
686	Same as above	$-C(=O)-O-CH_2-Ph$
687	Same as above	$-C(=O)-C(=O)-Ph$
688		$-CH_3$
689	Same as above	$-CH_2CH_3$
690	Same as above	$-C(=O)-CH_3$
691	Same as above	$-CH_2-Ph$
692	Same as above	$-C(=O)-Ph$
693	Same as above	$-C(=O)-O-CH_2-Ph$
694	Same as above	$-C(=O)-C(=O)-Ph$
695		$-CH_3$
696	Same as above	$-CH_2CH_3$
697	Same as above	$-C(=O)-CH_3$
698	Same as above	$-CH_2-Ph$
699	Same as above	$-C(=O)-Ph$
700	Same as above	$-C(=O)-O-CH_2-Ph$
701	Same as above	$-C(=O)-C(=O)-Ph$

Compounds 702-736 have the formula:

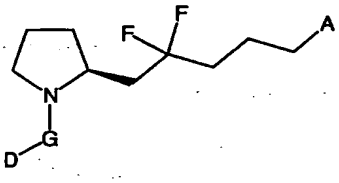


, with the individual variables defined in the table below.

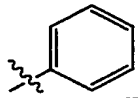
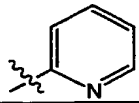
Cmpd #	A	-(G)$_x$-D
702		$-CH_3$
703	Same as above	$-CH_2CH_3$
704	Same as above	$-C(=O)-CH_3$
705	Same as above	$-CH_2$-Ph
706	Same as above	$-C(=O)$-Ph
707	Same as above	$-C(=O)-O-CH_2$-Ph
708	Same as above	$-C(=O)-C(=O)$-Ph
709		$-CH_3$
710	Same as above	$-CH_2CH_3$
711	Same as above	$-C(=O)-CH_3$
712	Same as above	$-CH_2$-Ph
713	Same as above	$-C(=O)$-Ph
714	Same as above	$-C(=O)-O-CH_2$-Ph
715	Same as above	$-C(=O)-C(=O)$-Ph
716		$-CH_3$
717	Same as above	$-CH_2CH_3$
718	Same as above	$-C(=O)-CH_3$
719	Same as above	$-CH_2$-Ph
720	Same as above	$-C(=O)$-Ph
721	Same as above	$-C(=O)-O-CH_2$-Ph
722	Same as above	$-C(=O)-C(=O)$-Ph
723		$-CH_3$
724	Same as above	$-CH_2CH_3$

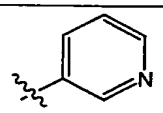
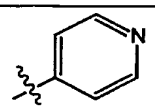
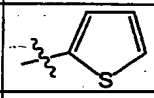
Cmpd #	A	-(G)$_x$-D
725	Same as above	-C(=O)-CH_3
726	Same as above	-CH_2-Ph
727	Same as above	-C(=O)-Ph
728	Same as above	-C(=O)-O-CH_2-Ph
729	Same as above	-C(=O)-C(=O)-Ph
730		-CH_3
731	Same as above	-CH_2CH_3
732	Same as above	-C(=O)-CH_3
733	Same as above	-CH_2-Ph
734	Same as above	-C(=O)-Ph
735	Same as above	-C(=O)-O-CH_2-Ph
736	Same as above	-C(=O)-C(=O)-Ph

Compounds 737-771 have the formula:



, with the individual variables defined in the table below.

Cmpd #	A	-(G)$_x$-D
737		-CH_3
738	Same as above	-CH_2CH_3
739	Same as above	-C(=O)-CH_3
740	Same as above	-CH_2-Ph
741	Same as above	-C(=O)-Ph
742	Same as above	-C(=O)-O-CH_2-Ph
743	Same as above	-C(=O)-C(=O)-Ph
744		-CH_3
745	Same as above	-CH_2CH_3
746	Same as above	-C(=O)-CH_3
747	Same as above	-CH_2-Ph
748	Same as above	-C(=O)-Ph
749	Same as above	-C(=O)-O-CH_2-Ph
750	Same as above	-C(=O)-C(=O)-Ph

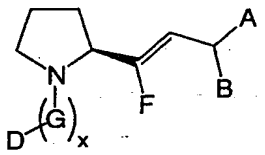
Cmpd #	A	-(G)$_x$-D
751		$-CH_3$
752	Same as above	$-CH_2CH_3$
753	Same as above	$-C(=O)-CH_3$
754	Same as above	$-CH_2$-Ph
755	Same as above	$-C(=O)$-Ph
756	Same as above	$-C(=O)-O-CH_2$-Ph
757	Same as above	$-C(=O)-C(=O)$-Ph
758		$-CH_3$
759	Same as above	$-CH_2CH_3$
760	Same as above	$-C(=O)-CH_3$
761	Same as above	$-CH_2$-Ph
762	Same as above	$-C(=O)$-Ph
763	Same as above	$-C(=O)-O-CH_2$-Ph
764	Same as above	$-C(=O)-C(=O)$-Ph
765		$-CH_3$
766	Same as above	$-CH_2CH_3$
767	Same as above	$-C(=O)-CH_3$
768	Same as above	$-CH_2$-Ph
769	Same as above	$-C(=O)$-Ph
770	Same as above	$-C(=O)-O-CH_2$-Ph
771	Same as above	$-C(=O)-C(=O)$-Ph

EXAMPLE 5

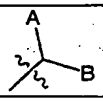
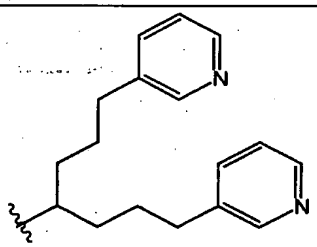
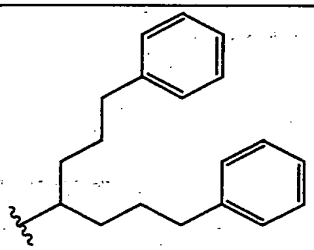
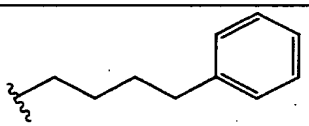
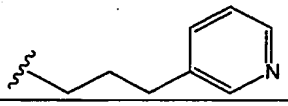
Compounds 772-967

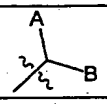
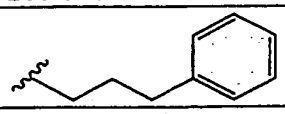
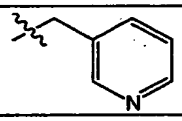
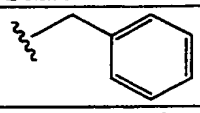
Compounds 772- are synthesized via the method set forth in Scheme 5, above.

Compounds 772-820 have the formula:

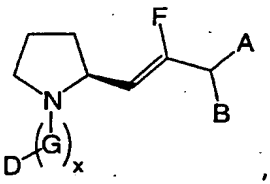


, with the individual variables defined in the table below

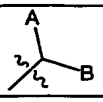
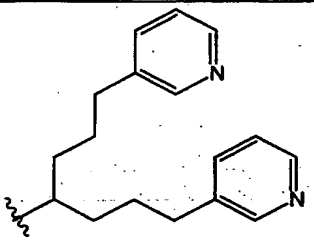
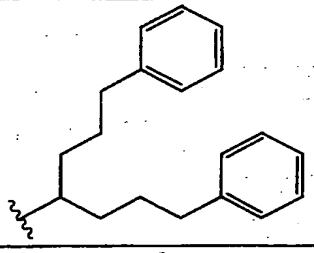
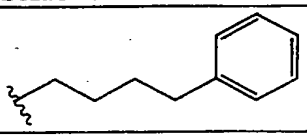
Cmpd #		$-(G)_x-D$
772		$-CH_3$
773	Same as above	$-CH_2CH_3$
774	Same as above	$-C(=O)-CH_3$
775	Same as above	$-CH_2-Ph$
776	Same as above	$-C(=O)-Ph$
777	Same as above	$-C(=O)-O-CH_2-Ph$
778	Same as above	$-C(=O)-C(=O)-Ph$
779		$-CH_3$
780	Same as above	$-CH_2CH_3$
781	Same as above	$-C(=O)-CH_3$
782	Same as above	$-CH_2-Ph$
783	Same as above	$-C(=O)-Ph$
784	Same as above	$-C(=O)-O-CH_2-Ph$
785	Same as above	$-C(=O)-C(=O)-Ph$
786		$-CH_3$
787	Same as above	$-CH_2CH_3$
788	Same as above	$-C(=O)-CH_3$
789	Same as above	$-CH_2-Ph$
790	Same as above	$-C(=O)-Ph$
791	Same as above	$-C(=O)-O-CH_2-Ph$
792	Same as above	$-C(=O)-C(=O)-Ph$
793		$-CH_3$

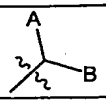
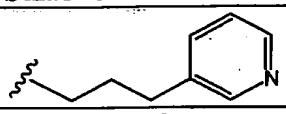
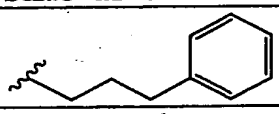
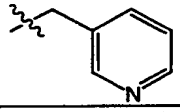
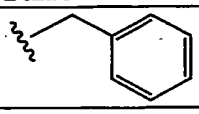
Cmpd #		-(G)$_x$-D
794	Same as above	-CH_2CH_3
795	Same as above	-C(=O)-CH_3
796	Same as above	-CH_2-Ph
797	Same as above	-C(=O)-Ph
798	Same as above	-C(=O)-O-CH_2-Ph
799	Same as above	-C(=O)-C(=O)-Ph
800		-CH_3
801	Same as above	-CH_2CH_3
802	Same as above	-C(=O)-CH_3
803	Same as above	-CH_2-Ph
804	Same as above	-C(=O)-Ph
805	Same as above	-C(=O)-O-CH_2-Ph
806	Same as above	-C(=O)-C(=O)-Ph
807		-CH_3
808	Same as above	-CH_2CH_3
809	Same as above	-C(=O)-CH_3
810	Same as above	-CH_2-Ph
811	Same as above	-C(=O)-Ph
812	Same as above	-C(=O)-O-CH_2-Ph
813	Same as above	-C(=O)-C(=O)-Ph
814		-CH_3
815	Same as above	-CH_2CH_3
816	Same as above	-C(=O)-CH_3
817	Same as above	-CH_2-Ph
818	Same as above	-C(=O)-Ph
819	Same as above	-C(=O)-O-CH_2-Ph
820	Same as above	-C(=O)-C(=O)-Ph

Compounds 821-869 have the formula:

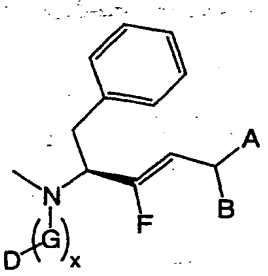


, with the individual variables defined in the table below

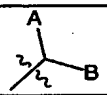
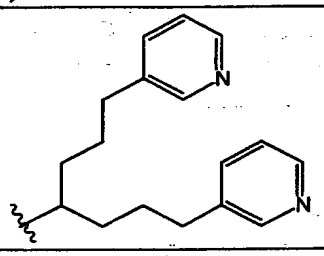
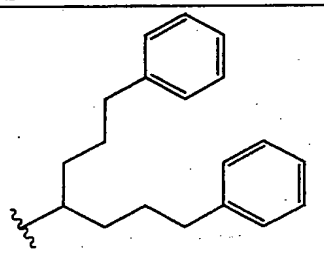
Cmpd #		$-(G)_x-D$
821		$-CH_3$
822	Same as above	$-CH_2CH_3$
823	Same as above	$-C(=O)-CH_3$
824	Same as above	$-CH_2-Ph$
825	Same as above	$-C(=O)-Ph$
826	Same as above	$-C(=O)-O-CH_2-Ph$
827	Same as above	$-C(=O)-C(=O)-Ph$
828		$-CH_3$
829	Same as above	$-CH_2CH_3$
830	Same as above	$-C(=O)-CH_3$
831	Same as above	$-CH_2-Ph$
832	Same as above	$-C(=O)-Ph$
833	Same as above	$-C(=O)-O-CH_2-Ph$
834	Same as above	$-C(=O)-C(=O)-Ph$
835		$-CH_3$
836	Same as above	$-CH_2CH_3$
837	Same as above	$-C(=O)-CH_3$

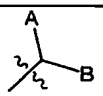
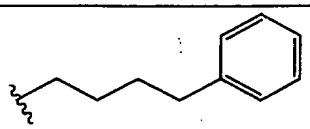
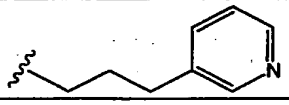
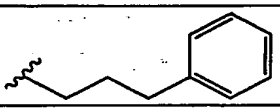
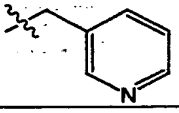
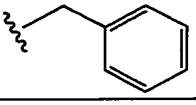
Cmpd #		-(G)$_x$-D
838	Same as above	-CH_2-Ph
839	Same as above	-C(=O)-Ph
840	Same as above	-C(=O)-O-CH_2-Ph
841	Same as above	-C(=O)-C(=O)-Ph
842		-CH_3
843	Same as above	-CH_2CH_3
844	Same as above	-C(=O)-CH_3
845	Same as above	-CH_2-Ph
846	Same as above	-C(=O)-Ph
847	Same as above	-C(=O)-O-CH_2-Ph
848	Same as above	-C(=O)-C(=O)-Ph
849		-CH_3
850	Same as above	-CH_2CH_3
851	Same as above	-C(=O)-CH_3
852	Same as above	-CH_2-Ph
853	Same as above	-C(=O)-Ph
854	Same as above	-C(=O)-O-CH_2-Ph
855	Same as above	-C(=O)-C(=O)-Ph
856		-CH_3
857	Same as above	-CH_2CH_3
858	Same as above	-C(=O)-CH_3
859	Same as above	-CH_2-Ph
860	Same as above	-C(=O)-Ph
861	Same as above	-C(=O)-O-CH_2-Ph
862	Same as above	-C(=O)-C(=O)-Ph
863		-CH_3
864	Same as above	-CH_2CH_3
865	Same as above	-C(=O)-CH_3
866	Same as above	-CH_2-Ph
867	Same as above	-C(=O)-Ph
868	Same as above	-C(=O)-O-CH_2-Ph
869	Same as above	-C(=O)-C(=O)-Ph

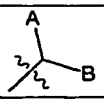
Compounds 870-918 have the formula:



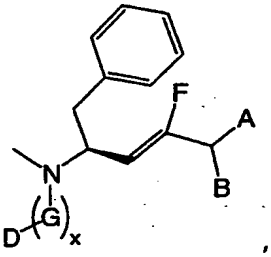
, with the individual variables defined in the table below

Cmpd #		$-(G)_x-D$
870		$-CH_3$
871	Same as above	$-CH_2CH_3$
872	Same as above	$-C(=O)-CH_3$
873	Same as above	$-CH_2-Ph$
874	Same as above	$-C(=O)-Ph$
875	Same as above	$-C(=O)-O-CH_2-Ph$
876	Same as above	$-C(=O)-C(=O)-Ph$
877		$-CH_3$
878	Same as above	$-CH_2CH_3$
879	Same as above	$-C(=O)-CH_3$
880	Same as above	$-CH_2-Ph$
881	Same as above	$-C(=O)-Ph$
882	Same as above	$-C(=O)-O-CH_2-Ph$
883	Same as above	$-C(=O)-C(=O)-Ph$

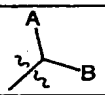
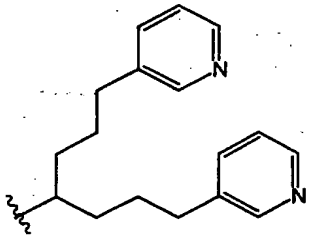
Cmpd #		-(G)$_x$-D
884		$-CH_3$
885	Same as above	$-CH_2CH_3$
886	Same as above	$-C(=O)-CH_3$
887	Same as above	$-CH_2$-Ph
888	Same as above	$-C(=O)$-Ph
889	Same as above	$-C(=O)-O-CH_2$-Ph
890	Same as above	$-C(=O)-C(=O)$-Ph
891		$-CH_3$
892	Same as above	$-CH_2CH_3$
893	Same as above	$-C(=O)-CH_3$
894	Same as above	$-CH_2$-Ph
895	Same as above	$-C(=O)$-Ph
896	Same as above	$-C(=O)-O-CH_2$-Ph
897	Same as above	$-C(=O)-C(=O)$-Ph
898		$-CH_3$
899	Same as above	$-CH_2CH_3$
900	Same as above	$-C(=O)-CH_3$
901	Same as above	$-CH_2$-Ph
902	Same as above	$-C(=O)$-Ph
903	Same as above	$-C(=O)-O-CH_2$-Ph
904	Same as above	$-C(=O)-C(=O)$-Ph
905		$-CH_3$
906	Same as above	$-CH_2CH_3$
907	Same as above	$-C(=O)-CH_3$
908	Same as above	$-CH_2$-Ph
909	Same as above	$-C(=O)$-Ph
910	Same as above	$-C(=O)-O-CH_2$-Ph
911	Same as above	$-C(=O)-C(=O)$-Ph
912		$-CH_3$
913	Same as above	$-CH_2CH_3$

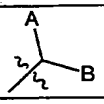
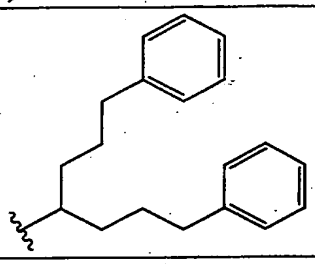
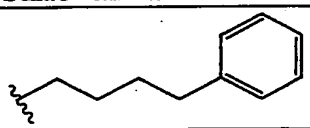
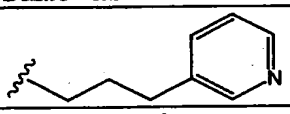
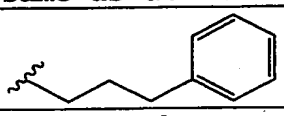
Cmpd #		-(G)$_x$-D
914	Same as above	-C(=O)-CH_3
915	Same as above	-CH_2-Ph
916	Same as above	-C(=O)-Ph
917	Same as above	-C(=O)-O-CH_2-Ph
918	Same as above	-C(=O)-C(=O)-Ph

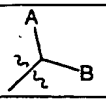
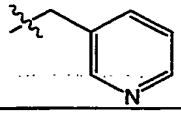
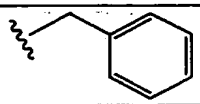
Compounds 919-967 have the formula:



, with the individual variables defined in the table below

Cmpd #		-(G)$_x$-D
919		-CH_3
920	Same as above	-CH_2CH_3
921	Same as above	-C(=O)-CH_3
922	Same as above	-CH_2-Ph
923	Same as above	-C(=O)-Ph
924	Same as above	-C(=O)-O-CH_2-Ph
925	Same as above	-C(=O)-C(=O)-Ph

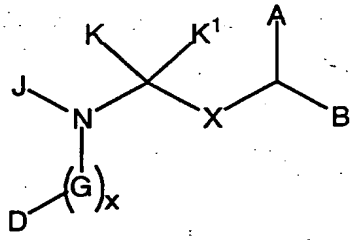
Cmpd #		$-(G)_x-D$
926		$-CH_3$
927	Same as above	$-CH_2CH_3$
928	Same as above	$-C(=O)-CH_3$
929	Same as above	$-CH_2-Ph$
930	Same as above	$-C(=O)-Ph$
931	Same as above	$-C(=O)-O-CH_2-Ph$
932	Same as above	$-C(=O)-C(=O)-Ph$
933		$-CH_3$
934	Same as above	$-CH_2CH_3$
935	Same as above	$-C(=O)-CH_3$
936	Same as above	$-CH_2-Ph$
937	Same as above	$-C(=O)-Ph$
938	Same as above	$-C(=O)-O-CH_2-Ph$
939	Same as above	$-C(=O)-C(=O)-Ph$
940		$-CH_3$
941	Same as above	$-CH_2CH_3$
942	Same as above	$-C(=O)-CH_3$
943	Same as above	$-CH_2-Ph$
944	Same as above	$-C(=O)-Ph$
945	Same as above	$-C(=O)-O-CH_2-Ph$
946	Same as above	$-C(=O)-C(=O)-Ph$
947		$-CH_3$
948	Same as above	$-CH_2CH_3$
949	Same as above	$-C(=O)-CH_3$
950	Same as above	$-CH_2-Ph$
951	Same as above	$-C(=O)-Ph$
952	Same as above	$-C(=O)-O-CH_2-Ph$
953	Same as above	$-C(=O)-C(=O)-Ph$

Cmpd #		$-(G)_x-D$
954		$-CH_3$
955	Same as above	$-CH_2CH_3$
956	Same as above	$-C(=O)-CH_3$
957	Same as above	$-CH_2$-Ph
958	Same as above	$-C(=O)$-Ph
959	Same as above	$-C(=O)-O-CH_2$-Ph
960	Same as above	$-C(=O)-C(=O)$-Ph
961		$-CH_3$
962	Same as above	$-CH_2CH_3$
963	Same as above	$-C(=O)-CH_3$
964	Same as above	$-CH_2$-Ph
965	Same as above	$-C(=O)$-Ph
966	Same as above	$-C(=O)-O-CH_2$-Ph
967	Same as above	$-C(=O)-C(=O)$-Ph

While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products, processes and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.

CLAIMS

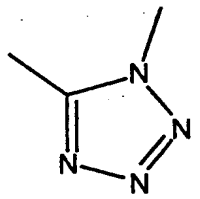
1. A compound having formula (I):



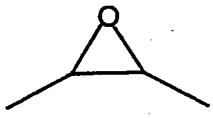
(I)

and pharmaceutically acceptable derivatives thereof, wherein:

X is selected from $-CH_2CH_2-$, $-CH=CH-$, $-C(OH)CH_2-$, $-CH_2C(OH)-$, $=C(F)CH_2-$, $-C(F)=CH_2-$, $-NHC(O)-$, $-P(O)(OH)CH_2-$, $-CH_2SO_2-$, $-C(S)NR^1-$, $-C(O)CH_2CH(OH)-$, $-C(OH)CF_2-$, $-C(O)CF_2-$, $-CH(F)CH_2-$, $-C(F)_2CH_2-$,



or



A, B and R^1 are independently E, (C_1-C_{10})-straight or branched alkyl, (C_2-C_{10})-straight or branched alkenyl or alkynyl, or (C_5-C_7)-cycloalkyl or cycloalkenyl; wherein 1 or 2 hydrogen atoms in said alkyl, alkenyl or alkynyl are optionally and independently replaced with E, (C_5-C_7)-cycloalkyl or cycloalkenyl; and wherein 1 to 2 of the $-CH_2-$ groups in said alkyl, alkenyl, or alkynyl groups is optionally and independently replaced by -O-, -S-, $-S(O)-$, $-S(O)_2-$, =N-, -N= or $-N(R^3)-$;

or, B and R^1 are independently hydrogen;

R^3 is hydrogen, (C_1-C_4)-straight or branched alkyl, (C_3-C_4)-straight or branched alkenyl or alkynyl, or (C_1-C_4) bridging alkyl, wherein a bridge is formed between the nitrogen atom to which said R^3 is bound and any carbon atom of said alkyl, alkenyl or alkynyl to form a ring, and wherein said ring is optionally benzofused;

E is a saturated, partially saturated or unsaturated, or aromatic monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms independently selected from C, N, $N(R^3)$, O, S, S(O), or $S(O)_2$; and wherein no more than 4 ring atoms are selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$;

wherein 1 to 4 hydrogen atoms in E are optionally and independently replaced with halogen, hydroxyl, hydroxymethyl, nitro, SO_3H, trifluoromethyl, trifluoromethoxy, (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl, O-[(C_1-C_6)-straight or branched alkyl], O-[(C_3-C_6)-straight or branched alkenyl], $(CH_2)_n-N(R^4)(R^5)$, $(CH_2)_n-NH(R^4)-(CH_2)_n-Z$, $(CH_2)_n-N(R^4-(CH_2)_n-Z)(R^5-(CH_2)_n-Z)$, $(CH_2)_n-Z$, $O-(CH_2)_n-Z$, $(CH_2)_n-O-Z$, $S-(CH_2)_n-Z$, CH=CH-Z, 1,2-methylenedioxy, C(O)OH, C(O)O-[(C_1-C_6)-straight or branched alkyl], $C(O)O-(CH_2)_n-Z$ or $C(O)-N(R^4)(R^5)$;

each of R^4 and R^5 are independently hydrogen, (C_1-C_6)-straight or branched alkyl, (C_3-C_5)-straight or branched alkenyl, or wherein R^4 and R^5, when bound to the same nitrogen atom, are taken together with the nitrogen atom to form a 5 or 6 membered ring, wherein said ring optionally contains 1 to 3 additional heteroatoms independently selected from N, $N(R^3)$, O, S, S(O), or

$S(O)_2$; wherein said alkyl, alkenyl or alkynyl groups in R_4 and R_5 are optionally substituted with Z.

each n is independently 0 to 4;

each Z is independently selected from a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms independently selected from C, N, $N(R^3)$, O, S, S(O), or $S(O)_2$; and wherein no more than 4 ring atoms are selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$;

wherein 1 to 4 hydrogen atoms in Z are optionally and independently replaced with halo, hydroxy, nitro, cyano, C(O)OH, (C_1-C_3)-straight or branched alkyl, O-(C_1-C_3)-straight or branched alkyl, C(O)O-[(C_1-C_3)-straight or branched alkyl], amino, NH[(C_1-C_3)-straight or branched alkyl], or N-[(C_1-C_3)-straight or branched alkyl]$_2$;

J is H, methyl, ethyl or benzyl;

K and K^1 are independently selected from (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl or alkynyl, or cyclohexylmethyl, wherein 1 to 2 hydrogen atoms in said alkyl, alkenyl or alkynyl is optionally and independently replaced with E;

wherein K and K^1 are independently and optionally substituted with up to 3 substituents selected from halogen, OH, O-(C_1-C_6)-alkyl, O-(CH_2)n-Z, NO_2, C(O)OH, C(O)-O-(C_1-C_6)-alkyl, $C(O)NR^4R^5$, NR^4R^5 and $(CH_2)_n$-Z; or,

J and K, taken together with the nitrogen and carbon atom to which they are respectively bound, form a 5-7 membered heterocyclic ring, optionally containing up to 3 additional heteroatoms selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$, wherein 1 to 4 hydrogen atoms in said

heterocyclic ring are optionally and independently replaced with (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl or alkynyl, oxo, hydroxyl or Z; and wherein any $-CH_2-$ group in said alkyl, alkenyl or alkynyl substituent is optionally and independently replaced by -O-, -S-, -S(O)-, $-S(O_2)-$, =N-, -N=, or $-N(R^3)-$; and wherein said heterocyclic ring is optionally fused with E;

G, when present, is $-S(O)_2-$, -C(O)-, $-S(O)_2-Y-$, -C(O)-Y-, -C(O)-C(O)-, or -C(O)-C(O)-Y-;

Y is oxygen, or $N(R^6)$;

wherein R^6 is hydrogen, E, (C_1-C_6)-straight or branched alkyl, (C_3-C_6)-straight or branched alkenyl or alkynyl; or wherein R^6 and D are taken together with the atoms to which they are bound to form a 5 to 7 membered ring system wherein said ring optionally contains 1 to 3 additional heteroatoms independently selected from O, S, N, $N(R^3)$, SO, or SO_2; and wherein said ring is optionally benzofused;

D is hydrogen, (C_1-C_7)-straight or branched alkyl, (C_2-C_7)-straight or branched alkenyl or alkynyl, (C_5-C_7)-cycloalkyl or cycloalkenyl optionally substituted with (C_1-C_6)-straight or branched alkyl or (C_2-C_7)-straight or branched alkenyl or alkynyl, [(C_1-C_7)-alkyl]-E, [(C_2-C_7)-alkenyl or alkynyl]-E, or E;

wherein 1 to 2 of the CH_2 groups of said alkyl, alkenyl or alkynyl chains in D is optionally replaced by -O-, -S-, -S(O)-, $-S(O_2)-$, =N-, -N=, or $-N(R^3)$;

provided that when J is hydrogen or G is selected from $-S(O)_2-$, C(O)C(O)-, SO_2-Y, C(O)-Y, or C(O)C(O)-Y, wherein Y is O; then D is not hydrogen; and

x is 0 or 1.

2. The compound according to claim 1, wherein:

each of A and B is independently selected from $-CH_2-CH_2-E$ or $-CH_2-CH_2-CH_2-E$; and

E is a monocyclic or bicyclic aromatic ring system, wherein said ring comprises 5-7 ring atoms independently selected from C, N, $N(R^3)$, O, S, S(O), or $S(O)_2$, and wherein 1 to 4 ring atoms are independently selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$;

wherein 1 to 4 hydrogen atoms in E are optionally and independently replaced with halogen, hydroxyl, hydroxymethyl, nitro, SO_3H, trifluoromethyl, trifluoromethoxy, (C_1-C_6)-straight or branched alkyl, (C_2-C_6)-straight or branched alkenyl, O-[(C_1-C_6)-straight or branched alkyl], O-[(C_3-C_6)-straight or branched alkenyl], $(CH_2)_n-N(R^4)(R^5)$, $(CH_2)_n-NH(R^4)-(CH_2)_n-Z$, $(CH_2)_n-N(R^4-(CH_2)_n-Z)(R^5-(CH_2)_n-Z)$, $(CH_2)_n-Z$, $O-(CH_2)_n-Z$, $(CH_2)_n-O-Z$, $S-(CH_2)_n-Z$, CH=CH-Z, 1,2-methylenedioxy, C(O)OH, or $C(O)-N(R^4)(R^5)$.

3. The compound according to claim 1 or 2, wherein D is an aromatic monocyclic or bicyclic ring system, wherein each ring comprises 5 to 7 ring atoms independently selected from C, N, $N(R^3)$, O, S, S(O), or $S(O)_2$; and wherein no more than 4 ring atoms are selected from N, $N(R^3)$, O, S, S(O), or $S(O)_2$.

4. The compound according to claim 3,

wherein:

D is phenyl; and

x is 1.

5. The compound according to claim 4, wherein G is -C(O)C(O)-.

6. The compound according to claim 4, wherein G is $-SO_2-$.

7. The compound according to claim 4, wherein G is -C(O)-.

8. The compound according to claim 4, wherein G is -C(O)Y-.

9. The compound according to claim 1 or 2, wherein:

x is 0;

D is selected from (C_1-C_5)-straight or branched alkyl, or [(C_1-C_3)-straight or branched alkyl)]-E; and

E is an aromatic monocyclic or bicyclic ring system, wherein in said ring system each ring comprises 5 to 7 ring atoms independently selected from C, N, N(R^3), O, S, S(O), or $S(O)_2$; and wherein no more than 4 ring atoms are selected from N, N(R^3), O, S, S(O), or $S(O)_2$.

10. The compound according to claim 9, wherein E is phenyl.

11. The compound according to claim 2, wherein each of A and B is independently selected from $-CH_2-CH_2-E$ or $-CH_2-CH_2-CH_2-E$; and

E is pyridyl.

12. A composition comprising a compound according to claim 1 and a pharmaceutically effective carrier.

13. The composition according to claim 12, further comprising a neurotrophic factor.

14. The composition according to claim 13, wherein said neurotrophic factor is selected from nerve growth factor (NGF), insulin-like growth factor (IGF-1) and its active truncated derivatives such as gIGF-1 and Des(1-3)IGF-I, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factors (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3)and neurotrophin 4/5 (NT-4/5).

15. The composition according to claim 14, wherein said neurotrophic factor is nerve growth factor (NGF).

16. A method for stimulating neuronal regeneration or preventing neurodegeneration in a patient or in an *ex vivo* nerve cell, comprising the step of

administering to said patient or said nerve cell a compound according to any one of claims 1-12.

17. The method according to claim 16, wherein said compound is administered to a patient and is formulated together with a pharmaceutically suitable carrier into a pharmaceutically acceptable composition.

18. The method according to claim 17, comprising the additional step of administering to said patient a neurotrophic factor either as part of a multiple dosage form together with said compound or as a separate dosage form.

19. The method according to claim 18, wherein said neurotrophic factor is selected from nerve growth factor (NGF), insulin-like growth factor (IGF-1) and its active truncated derivatives such as gIGF-1 and Des(1-3)IGF-I, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factors (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3)and neurotrophin 4/5 (NT-4/5).

20. The method according to claim 19, wherein said neurotrophic factor is nerve growth factor (NGF).

21. The method according to claim 16, wherein said method is used to treat a patient suffering from a disease selected from trigeminal neuralgia,

glosspharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, muscle injury, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured, or prolapsed invertebrae disk syndrome's, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, such as those caused by lead, dapsone, ticks, or porphyria, other peripheral myelin disorders, Alzheimer's disease, Gullain-Barre syndrome, Parkinson's disease and other Parkinsonian disorders, ALS, Tourette's syndrome, multiple sclerosis, other central myelin disorders, stroke and ischemia associated with stroke, neural paropathy, other neural degenerative diseases, motor neuron diseases, sciatic crush, neuropathy associated with diabetes, spinal cord injuries, facial nerve crush and other trauma, chemotherapy- and other medication-induced neuropathies, and Huntington's disease.

22. The method according to claim 16, wherein said method is used to stimulate neuronal regeneration in an *ex vivo* nerve cell.

23. The method according to claim 22, comprising the additional step of contacting said *ex vivo* nerve cell with a neurotrophic factor.

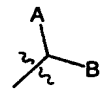
24. The method according to claim 23, wherein said neurotrophic factor is selected from nerve growth factor (NGF), insulin-like growth factor (IGF-1) and its active truncated derivatives such as gIGF-1 and

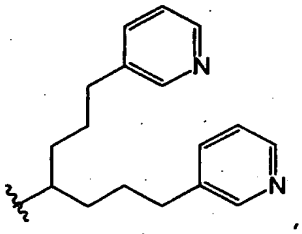
Des(1-3)IGF-I, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factors (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3)and neurotrophin 4/5 (NT-4/5).

25. The method according to claim 24, wherein said neurotrophic factor is nerve growth factor (NGF).

26. The compound according to claim 1, wherein:

$-(G)_x-D$ is selected from $-CH_3$, $-CH_2CH_3$, $-C(=O)-CH_3$, $-CH_2-Ph$, $-C(=O)-Ph$, $-C(=O)-O-CH_2-Ph$ or $-C(=O)-C(=O)-Ph$, wherein Ph is phenyl; and



is selected from 

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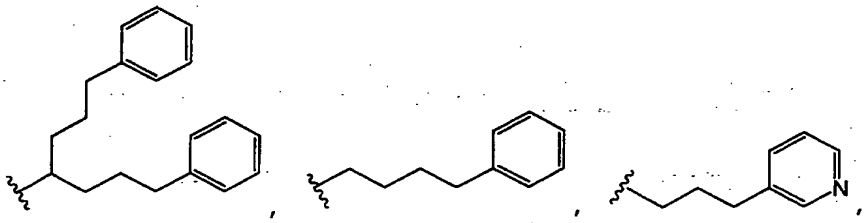

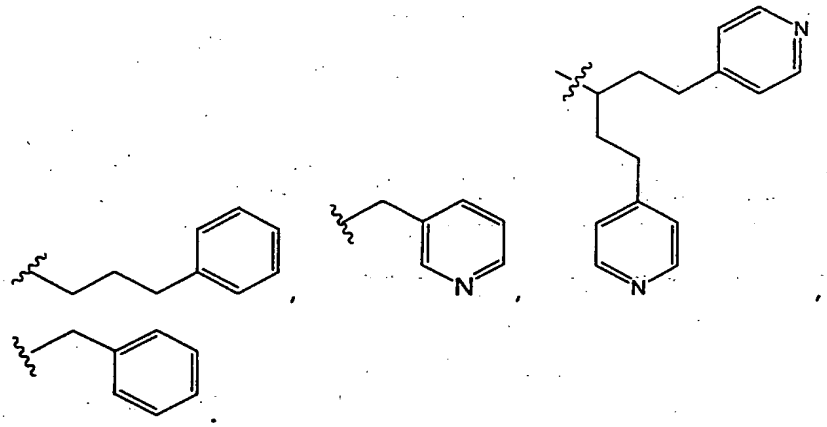

, or

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20491

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/256, 276.4, 264, 265; 548/530, 533, 540; 564/343, 384; 514/333, 343, 341, 423, 422, 408, 427, 332, 327, 330

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,840,736 A (ZELLE et al.) 24 November 1998, columns 2-5.	1-12, 16-17, 21-22, 26
X,P — Y,P	US 6,004,993 A (STEINER et al.) 21 December 1999, col. 6, lines 35-45, col. 14, Table I.	1-10, 12, 16-17, 21-22, 26 ----- 1-10, 12, 16-17, 21-22, 26
X,P — Y,P	Database CA on STN. Chem. abst. Vol. 132, (Columbus, OH, USA), abstract No. 237375, LI et al. "Preparation of bridged heterocyclic derivatives for treatment of neurological and other disorders" WO 20000016603, 03 March 2000, see entire abstract.	1-10, 12, 16-17, 21-22, 26 ----- 1-10, 12, 16-17, 21-22, 26

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 08 NOVEMBER 2000	Date of mailing of the international search report 15 DEC 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JANE FAN Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20491

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P -- Y,P	Database CA on STN. Chem. abstr. Vol. 132, 2000, (Columbus, OH, USA), abstract No. 175850, ROSS et al." Compositions and uses for vision and memory disorders", WO 2000009108, 18 May 2000, see entire abstract.	1-10, 12, 16-17, 21-22, 26 ---- 1-10, 12, 16-17, 21-22, 26
X -- Y	US 5,721,256 A (HAMILTON et al.) 24 February 1998, see entire document, especially col.2, lines 55-67.	1-10, 12, 16-17, 21-22, 26 --- 1-10, 12, 16-17, 21-22, 26
X -- Y	US 5,744,485 A (ZELLE et al.) 28 April 1998, see entire document, especially col. 2, lines 50-67.	1-10, 12, 16-17, 21-22, 26 ---- 1-10, 12, 16-17, 21-22, 26
X,P -- Y,P	US 5,945,441 A (STEINER et al.) 31 August 1999, see entire document especially col. 3	1-10, 12, 16-17, 21-22, 26 ---- 1-10, 12, 16-17, 21-22, 26
X -- Y	US 5,786,378 A (HAMILTON et al.) 28 July 1998, see entire document especially col.3.	1-10, 12, 16-17, 21-22, 26 --- 1-10, 12, 16-17, 21-22, 26
X,P -- Y,P	US 5,990,131 A (HAMILTON et al.) 23 November 1999, see entire document.	1-10, 12, 16-17, 21-22, 26 ----- 1-10, 12, 16-17, 21-22, 26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20491

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-12,16-17,21-22,26

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20491

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

IPC7 A61K 31/445, 38/18, 31/40, 31/44; C07D 207/06, 211/06, 211/32

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

546/256, 276.4, 264, 265; 548/530, 533, 540; 564/343, 384; 514/333, 343, 341, 423, 422, 408, 427, 332, 327, 330

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-12,16-17,21-22,26 (all in part), drawn to pyrrolidines (J-N-C-K form five memebered ring),no other hetero-ring containing (A,B,X all containing no hetero ring), compositions thereof and method of using.
Group II, claim(s)1-12,16-17,21-22,26 (all in part), drawn to pyrrolidines (J-N-C-K form five memebered ring),containing other hetero-ring (A,B,X containing hetero ring), compositions thereof and method of using.
Group III, claim(s)1-12,16-17,21-22,26 (all in part), drawn to tetrazoles (X is tetrazole) containing no other hetero-ring, compositions thereof and method of using.
Group IV, claim(s)1-12,16-17,21-22,26 (all in part), drawn to tetrazoles (X is tetrazole) containing other hetero-ring (A,B containing hetero-ring), compositions thereof and method of using.
Group V, claim(s)1-12,16-17,21-22,26 (all in part), drawn to non-heterocyclic compounds (A, B X, J, D, K all containing no hetero ring), compositions thereof and method of using.
Group VI, claims 1-12, 16-17, 21-22, 26(all in part), drawn to the remaining compounds.
Group VII ,claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group I further comprising a neurotrophic factor.
Group VIII ,claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group II further comprising a neurotrophic factor.
Group IX,claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group III further comprising a neurotrophic factor.
Group X, claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group IV further comprising a neurotrophic factor.
Group XI, claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group V further comprising a neurotrophic factor.
Group XII,claims 1-15, 18-20, 23-25, drawn to the method of using the compounds of group VI further comprising a neurotrophic factor.

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

1.For generic formula I, there is no common core which in the Markush Practice, is a significant structure element (only -C-) shared by all of the alternatives (J,G,D,K,K',X,A,B); See PCT Administrative Instructions Annex B Part I(f)(i)(B)(1)

2. Further, all alternatives do not belong to a recognized class of chemical compounds in the art to which the invention pertains. Note CA 1999:167033 pyridyl pyrolidines can be used for hair growth; CA 1999:110352 phenylalkylpyrrolidines can be used for diabetes; CA 97:104598 phenyl pyrrolidines can be used for bradykinin inhibitor

3.For method of using comprising an additional neurotrophic factor would cause synergistic effect.

Therefore, no linkage which form a single general inventive concept can be established among the different inventions.

If applicants do not elect, only group I will be searched.